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Association of Pediatric Hematology/Oncology Nurses

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

Updated Information Packet

2024–2026

Pediatric Chemotherapy and Biotherapy Provider Renewal

Updated Information Packet 2024-2026

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Acknowledgments

Since October 2004, APHON has trained more than 25,000 nurses as chemotherapy and biotherapy providers using *The Pediatric Chemotherapy and Biotherapy Curriculum*. In addition, APHON has trained more than 774 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 2 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.

Photobiomodulation for Oral Mucositis

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Learning Objectives:

1. Identify oral mucositis as a common dose-limiting side effect of cancer treatment for pediatric, adolescent, and young adult patients.
2. Discuss the mechanism of photobiomodulation in the reduction of inflammation.
3. Describe the barriers that should be addressed when developing a photobiomodulation program.

Oral mucositis, also known as stomatitis, is a significant dose-limiting side effect of cancer treatment for pediatric oncology patients (Gillard et al., 2019; Miller et al., 2012). Oral mucositis can range in severity and frequency depending on the treatment modality and regimen, with up to 80% incidence in children and adolescents/young adults (AYA) receiving chemotherapy or myeloablative hematopoietic stem cell transplant and as high as 99% occurrence in patients undergoing head and neck radiation therapy (Gillard et al., 2019; Hafner et al., 2023; Miller et al., 2012; Redman et al., 2022). As rapidly dividing cellular tissue, oral mucosa is highly sensitive to the destructive effects of chemotherapy and radiotherapy, with children and AYA potentially experiencing increased mucositis prevalence as compared to adults due to their higher epithelial mitotic rate (Hafner et al., 2023; Miller et al., 2012). The direct effect of radiation or chemotherapy halts oral epithelial cell renewal, which leads to localized tissue injury manifested with burning, erythema, and edema, and progressing to mucosal ulceration (Gillard et al., 2019; Miller et al., 2012; Pritchard et al., 2024). Oral mucositis commonly occurs 3-5 days after cytotoxic treatment initiation, with signs and symptoms of inflammation and ulceration peaking at 7-14 days (Gillard et al., 2019; Miller et al., 2012; Pritchard et al., 2024).

Oral mucositis decreases quality of life for patients and their caregivers as well as increases infection risk, prevents oral intake leading to dehydration and malnutrition, necessitates opioid analgesics for pain management, leads to increased hospital length of stay, and results in delayed treatment (Glass et al., 2022; Hafner et al., 2023; Miller et al., 2012; Pritchard et al., 2024; Redman et al., 2022). Historically, options for mucositis treatment and prophylaxis have been limited and include antimicrobial mouthwashes, strict oral hygiene, anti-inflammatory agents, cytoprotective agents, and cryotherapy (Glass et al., 2022; Hafner et al., 2023; Miller et al., 2012; Pritchard et al., 2024). However, recent studies on the use of low-level laser/light therapy, now known as photobiomodulation (PBM), have shown great

potential in oral mucositis treatment and prevention (Hafner et al., 2023) such that the use of intraoral PBM is now endorsed in the Children's Oncology Group (COG) Supportive Care Guidelines for pediatric patients undergoing HSCT and those receiving radiotherapy for head and neck cancers (COG, 2022).

What is Photobiomodulation?

Photobiomodulation (PBM) is the application of monochromatic low-level laser (or light-emitting diode [LED]) light in the red or near infrared spectrum (600nm – 1,000nm), and with a specific energy density, to promote tissue repair and regeneration, alleviate pain, and reduce inflammation (Huang et al., 2009; Pritchard et al., 2024; Thor Photomedicine Ltd., 2024). The light does not utilize an ablative or thermal action, but rather creates a photochemical effect wherein light is absorbed and exerts a chemical transformation (Huang et al., 2009).

The biological mechanism of PBM is on the cells' mitochondrial function. Mitochondria hold an important role in energy production and metabolism, using oxidative phosphorylation in the cellular respiratory chain to produce energy in the form of adenosine triphosphate (ATP; Huang et al., 2009). Mitochondria appear to be responsible for the cellular response to red and near infrared light, with the enzyme cytochrome c oxidase (COX) – an important aspect in ATP synthesis - serving as the primary photoacceptor for this light spectrum (Huang et al., 2009). In stressed or ischemic cells, mitochondria release excessive mitochondrial nitric oxide (mtMO) which binds to COX, competitively displaces oxygen, and results in reduced ATP production (Huang et al., 2009; Pritchard et al., 2024). Oxidative stress results in increased cellular inflammation and cell death, thus manifesting oral mucositis symptoms (Thor Photomedicine Ltd., 2024).

It is suggested that PBM of the correct wavelength and rate of energy delivery works by photodissociating mtNO from COX, thereby reversing the cellular respiration inhibition and reducing oxygen free radicals (Huang et al., 2009; Pritchard et al., 2024). The photostimulatory effects in mitochondrial processes lead to enhanced growth factor release and cell proliferation (Huang et al., 2009). This leads to decreasing inflammation as cell metabolism increases, with subsequent improvement in cell health and quicker resolution of oral mucositis symptoms (Pritchard et al., 2024; Thor Photomedicine Ltd., 2024).

PBM Limitations: Who Can Receive and Who Cannot?

Thor Photomedicine Ltd. (2024) identifies certain situations and patient populations in which PBM should be used with caution when incorporated into their plan of care, to include:

1. Do not use PBM over any known malignant lesions unless for pain relief during terminal stages of illness.

2. Avoid treating directly over a developing fetus. It may, however, be used on pregnant patients for back pain.
3. Thyroid: When treating over the thyroid, patients may experience increased heart rate. There is no evidence of harm and some evidence of benefit to treating Hashimoto's thyroiditis with PBM.
4. Tattoo: Treatment over a tattoo with higher irradiance laser may cause pain as the ink may absorb heat. If painful, pull back probe 15 mm from the surface of the skin.
5. Dark skin pigmentation: Occasionally some people with very dark skin pigmentation may feel an unpleasant sensation from the heat. If painful, pull probe 15 mm from the surface of the skin.

Implementing Photobiomodulation

While PBM has been recognized as a worthy intervention for oral mucositis treatment and prevention, it is not yet integrated as standard clinical practice due to lack of robust evidence and high quality clinical trials for determining PBM protocols (Hafner et al., 2023). Previous studies demonstrated a wide variety in PBM wavelength and energy density during administration, and there is inconsistency in treatment protocols, notably when to start PBM, how often to administer, and when to discontinue (Hafner et al., 2023; Pritchard et al., 2024; Redman et al., 2022). Additional obstacles for treatment centers to overcome include the outset cost of equipment, training, insurance reimbursement, and infrastructure to ensure laser safety and to sustain an ongoing program (Pritchard et al., 2024; Redman et al., 2022). However, two recent studies conducted in the United States by pediatric oncology treatment centers demonstrate efforts toward implementing PBM in clinical practice.

St. Jude Children's Research Hospital (SJCRH)

The research aim of the SJCRH study was to determine the feasibility and efficacy of PBM in the prevention and treatment of Grade 3 oral mucositis in patients undergoing HSCT for acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML; Pritchard et al., 2024). A secondary aim was to compare clinical manifestations (grade and duration of oral mucositis) associated with the development of oral mucositis between those treated with daily PBM and a matched control (Pritchard et al., 2024). Specially trained staff delivered PBM daily starting on the first day of conditioning therapy and continuing until engraftment (determined as absolute neutrophil count (ANC) ≥ 500 for two consecutive days) or day +20, and the treatment was delivered via an external probe and an intraoral probe (Pritchard et al., 2024).

Results indicated that patients treated with PBM demonstrated a significant decrease in duration of Grades 1 to 2 mucositis as well Grade 3 mucositis when compared to the untreated patient regardless of age, sex, race, or conditioning regimens (Pritchard et al., 2024). In addition to these findings, the total

days of hospitalization for patients treated with PBM (mean 32.4) was significantly lower (p = .009) when compared to the control (mean 40.2 days). The weighted average of those treated with PBM was ranked and compared to the control group. When compared to patients treated with PBM, the control group had significantly more (p = 0.03) severe mucositis than the patients treated with PBM (Pritchard et al., 2024).

West Virginia University Children's Hospital

At West Virginia University Children's Hospital, the study aim was to determine the impact of PBM on the use of oral and intravenous pain medications and the length of stay for patients admitted with oral mucositis (Glass et al., 2022). PBM protocols were initiated on the following populations: patients receiving high dose methotrexate; high-risk or very high-risk ALL during induction therapy; relapsed ALL patients; AML patients; patients receiving head or neck radiation; all lymphoma diagnoses; and any patient who verbalized mouth discomfort during or post treatment (Glass et al., 2022). PBM was added to the existing mucositis treatment protocol of a strict oral hygiene regimen including chlorhexidine gluconate 0.12% oral rinse twice daily and salt/soda mouth rinses four times per day. PBM treatment was administered by trained staff once every 24 hours to study participants on the inpatient unit, and outpatient participants were treated each visit to clinic. Results of the 19 patients who received PBM focused on mucositis and its side effects one year prior to implementation compared to post implementation. Findings included the following:

- Pain was controlled with oral narcotics but at a decreased use rate
- No use of patient-controlled analgesia narcotics
- No documented grade 3 or higher mucositis
- No documented tongue involvement
- Decrease in hospital length of stay from 11 days to 3 days
- Improvement in 95% of patients with mucositis even with an ANC < 500
- Resolution of mucositis within 24 to 48 hours
- Patient and parents were requesting PBM therapy.

The West Virginia University Children's Hospital study illustrates the benefits of adding PBM to the existing oral hygiene regimen with results demonstrating significant decrease in oral mucositis, decrease in admissions as well as hospital length of stay secondary to mucositis, decrease in the use of oral and intravenous opioid analgesics, and increase in patient and caregiver satisfaction (Glass et al., 2022).

Other Medical Uses for PBM Therapy

In addition to treating oral mucosa, PBM may have beneficial tissue effects in almost all tissues and organs of the human body (Huang et al., 2009). There are current protocols in use for adult patients experiencing skin breakdown, wound healing, radiation burns, graft-versus-host disease, joint swelling, pain, and prevention of chemotherapy-induced peripheral neuropathy along with many more supportive care treatments (Huang et al., 2009; Thor Photomedicine Ltd., 2024). Expanding research to include additional side effects experienced by pediatric oncology patients may demonstrate positive impacts in hospital length of stay, use of additional medications, and overall improved quality of life.

Conclusion

Evidence validates PBM as a feasible and effective complementary therapy in the treatment and prevention of oral mucositis for pediatric and AYA patients undergoing chemotherapy, radiation therapy, and HSCT, and has been endorsed within the COG Supportive Care Guidelines (COG, 2022). However, barriers to implementing PBM therapy, to include equipment purchase and supply costs, clinician/nurse training, and administration protocol development, prove to be a potent hindrance in making PBM a standard of care for pediatric oncology patients at this time.

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Infusion-Related Reaction

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Learner Outcomes

1. Explain two ways that the immune system is involved in infusion reactions
2. Differentiate between symptoms of allergic reactions, anaphylaxis, and cytokine release syndrome
3. Describe nursing management of an infusion reaction, including three drugs commonly used during infusion reactions

Introduction

According to the National Cancer Institute (NCI) an infusion-relayed reaction, (IRR) is classified as an adverse reaction to a pharmacological or biological infusion. The intravenous infusion of a foreign drug or substance into the human body creates the potential for an immune system reaction. Infusion-related reactions can be classified as either antibody-mediated or non-antibody-mediated. Antibody-mediated reactions are sometimes called immune-mediated reactions and non-antibody-mediated reactions are sometimes called non-immune-mediated reactions. This nomenclature can be confusing since the immune system is involved in both reactions. The difference is that antibody-mediated reactions primarily involve the adaptive immune system and non-antibody-mediated reactions involve mainly the innate immune system. (Polovich et al., 2014) For clarity in this article, we will refer to antibody-mediated and non-antibody-mediated responses.

An antibody-mediated reaction is a true allergic response to foreign proteins, involving immunoglobulin E (IgE) and the adaptive immune system. Non-antibody-mediated reactions involve processes of the innate immune system, such as cytokine release and inflammation. Most infusion-related reactions are minor and easily controlled, however some reactions can be more severe and even fatal without prompt intervention. Initial symptoms of antibody-mediated, and non-antibody-mediated infusion-related reactions are very similar, however, understanding each reaction and its underlying pathophysiology will improve decisions yielding a better outcome. (Vogel, 2010). Nurses involved in the intravenous, intramuscular, or subcutaneous administration of chemotherapy and biotherapy agents should be aware of the potential for infusion-related reactions for any drug being administered. Nurses

should also be aware of the difference between antibody-mediated and non-antibody-mediated infusion-related reactions. Being able to recognize the type of infusion-related reaction will guide appropriate response to the reaction that occurs.

Immune System Review

The immune system defends the body against foreign substances, cells, and tissues by producing a protective response when there is a perceived threat. The immune response can be innate, adaptive, or both. The innate immune response (neutrophils, natural killer cells, macrophages, and others is the body's first line of systemic defense. It is a non-specific defense mechanism that can respond immediately or within hours of exposure to a foreign substance. The innate response acts on the identification of general threats. Innate immunity is present prior to exposure to foreign substances (Solomon & Komanduri, 2001). Adaptive immunity, also referred to as acquired immunity, uses specific antibodies to mount an immune response to specific substances. Adaptive immunity is slower than innate immunity because it does not respond unless there is re-exposure to a specific antigen. The adaptive immune system uses memory to learn about the pathogen during first exposure. It creates a memory of that pathogen that will enhance the response against it during future encounters. These adaptive immune responses are directed by the B- and the T-lymphocytes. B-lymphocytes have cell-surface receptors that are trained to recognize the foreign proteins (antigens) from the self-proteins. This process mounts a slower more specific attack against the foreign proteins recognized. (Herring 2019) When an antigen is recognized from a previous exposure as undesirable, the B-lymphocytes respond by producing antibodies against that antigen. The B-cell antibody attaches to the antigen and marks the cell for destruction. T-lymphocytes respond to intracellular foreign substances (Solomon & Komanduri, 2001).

The immune system may “misinterpret” some medications or their components as foreign invaders and mount a defensive response against the presumed invader. This protective response can be mild or severe. The response can be an antigen-antibody reaction, or it can be a response by components of the innate immune system.

Anaphylaxis, Allergic Reaction, Cytokine Release, What Is the Difference?

When administering an anti-cancer therapy, it is important to be aware of the potential risk for any infusion-related reaction. These reactions can be antibody mediated allergic reactions (allergic reaction or anaphylaxis), or they can be non-antibody mediated reactions, such as cytokine release syndrome.

Below please refer to Table 1 which provides a detailed comparison between antibody mediated and non-antibody mediated infusion-related reactions. (Herring, 2019)

Table 1: Allergic reaction vs Anaphylaxis vs Cytokine Release Syndrome

	Allergic reaction (Mild to moderate hypersensitivity reaction)	Anaphylaxis (moderate to severe hypersensitivity reaction)	Subclinical Hypersensitivity	Cytokine Release Syndrome
Type of immune response	Antibody mediated, (humoral immune system)	Antibody mediated, (humoral immune system)	Antibody mediated, (humoral immune system)	Non-antibody mediated (innate immune system)
Symptoms	Skin: rash, urticaria, pruritis Localized reaction No cardiorespiratory symptoms	Respiratory compromise: SOB, wheezing, cyanosis, bronchospasm, respiratory arrest Circulatory compromise: increased heart rate, ↓BP, myocardial ischemia, cardiac arrest Neurological compromise: confusion, agitation, loss of consciousness Skin/mucosal: erythema, urticarial, periorbital and facial edema (angioedema) GI: nausea, vomiting, diarrhea	None (drug levels are below therapeutic range)	Fever and chills Nausea Dyspnea Throat/tongue swelling Rash Headache Tachycardia Hypotension
Timing	Within minutes or hours	Within minutes to hours after subsequent doses	After subsequent doses	Within minutes or hours of exposure to first dose (for CRS related to CAR-T therapy, the reaction may be days later)

Management	Stop infusion Administer PO, IM, IV Diphenhydramine (H2 antagonist) Famotidine (H1 antagonist) Premedicate prior to subsequent doses of the medication	Stop infusion Administer antihistamines, anti-inflammatories, epinephrine Diphenhydramine (H2 antagonist) Famotidine (H1 antagonist) Hydrocortisone Epinephrine (respiratory symptoms) Change to alternate form of drug Do not restart infusion Desensitization may be considered	Monitor asparaginase assay levels No need for medications, since no clinical symptoms May switch to alternate formulation	Stop infusion Administer antihistamines, anti-inflammatories, epinephrine Diphenhydramine (H2 antagonist) Famotidine (H1 antagonist) Hydrocortisone Epinephrine (respiratory symptoms) Change to alternate form of drug Infusion may be resumed, at a slower rate, after symptoms have resolved Premedicate with future infusions

What is an Allergic Reaction?

Allergic reactions are mild to moderate hypersensitivity reactions. During the initial exposure, IgE antibodies are produced and bind to receptors on mast cells and basophils. Allergic reactions can occur with subsequent doses. These reactions can be immediate, occurring within minutes of exposure. However, there can also be delayed reactions that may occur 10-12 hours after exposure. The quicker the onset the more severe the reaction will be.

Mild to moderate hypersensitivity reactions usually have dermatologic manifestations are puritis urticaria and skin flushing can occur in up to 90% of patients. and do not involve cardiac or respiratory symptoms. (Olsen et al., 2023). Infusion-related reactions can be categorized using a grading system based on the symptoms and the severity of the reaction. A careful detailed assessment will provide the information needed to determine the appropriate grade and management of subsequent doses of the drug. The NCI published *Common Terminology Criteria for Adverse Event*s (CTCAE version 5.0) which is used to grade all infusion-related reactions. This chart is presented later on in this article

What is Anaphylaxis?

Anaphylaxis is a moderate to severe hypersensitivity reaction involving an immediate overwhelming antibody-mediated systemic response. This may occur within seconds to minutes after the subsequent administration of a foreign protein. These reactions can be life threatening and need to be recognized and treated immediately to prevent severe outcome (Barroso et al., 2024). Anaphylaxis is a reaction which involves IgE mediated release of histamine and other mediators from mast cells and basophils. Anaphylaxis is a medical emergency that can result in respiratory failure, cardiovascular collapse, and death. The reactions during anaphylaxis can be unpredictable. The risk for anaphylaxis increases with any of the following:

- Agents are given at high doses
- Agents are given IV
- Agents are derived from bacteria (asparaginase, for example)
- Agent manufacturing methods leave impurities in the product
- Patients have had previous exposure to the agent

Anaphylaxis is an acute inflammatory reaction resulting in a more serious systemic reaction. These reactions can have multiple clinical manifestations. Table 2 adopted from (Herring, 2019) indicates the se clinical manifestations.

Table 2: Anaphylaxis Side Effects by System

Integumentary	pruritus, urticaria, erythema, angioedema
Respiratory	dyspnea, wheezing, cough, rhinitis, sneezing, hoarseness, tachypnea, chest tightness, hypoxemia, bronchospasm, laryngeal edema
Cardiovascular	warmth, flushing, dizziness, hypotension, chest tightness, palpitations, tachycardia, bradycardia, arrhythmia, ischemia, infarction, cardiac arrest, angioedema
Gastrointestinal	nausea, vomiting, diarrhea, metallic taste, abdominal pain, cramping
Neurologic	anxiety, dizziness, agitation, feeling of impending doom
Endocrine	rigors, diaphoresis, fever, generalized feeling of warmth
Musculoskeletal	arthralgias, myalgias, fatigue, hypotonia

Reaction Management associated with Chemotherapy and Biotherapy

Most therapies for cancer treatment are associated with some variation of a risk for reaction. This risk can differ depending on several factors: the agent being infused, rate of the infusion, tumor burden, as well as with each individual patient. One patient may tolerate therapy very well, yet another patient may have no tolerance for it. It is an individualized response. The onset of reactions will also vary depending on the agent and the patient. Below please find a chart that identifies the characteristics that are associated with major anti-cancer therapies. Knowing which drugs have a higher potential provide an opportunity to prepare and plan for what may occur. Table 3 provides a list of the predicted risk of immediate hypersensitivity reactions of chemotherapy agents.

Table 3. Characteristics of IRRs associated with major anticancer therapies

Drug	Incidence of IRRs	Onset of IRRs	Signs/symptoms of IRRs	Prophylaxis	Management
Chemotherapy					
Paclitaxel[3,30,31,39,47-53]	Albumin-bound: 4% without premedication. Cremophor-bound: 10% despite premedication.	On first exposure during cycle 1 or 2, within the first 10 min of infusion.	Nausea, vomiting, diarrhea, dyspnea, chest tightness, wheezing, throat tightness, bronchospasm, skin reactions, angioedema, urticaria, hypotension, tachycardia.	One dose of i.v. dexamethasone plus diphenhydramine (50 mg i.v.) and a H2 receptor antagonist (ranitidine 50 mg or cimetidine 300 mg i.v.) 30 min before the infusion.	Grade 1/2: stop or slow the infusion rate + symptomatic treatment. Grade 3/4: stop treatment + aggressive symptomatic treatment. Consider desensitization.
Docetaxel[3,15,30,39,46-48,52]	5% (2% severe) despite premedication. 30% without Premedication.	On first exposure during cycle 1 or 2, within the first 10 min of infusion.	Flushing, hypotension, dyspnea, bronchospasm, skin reactions, urticaria, pruritus, angioedema, tachycardia, chest or back pain, fluid retention.	Oral dexamethasone 8 mg bid for 3 days (starting 1 day before docetaxel administration) or 12, 3, and 1 h before the infusion.	Grade 1/2: stop or slow the infusion rate + symptomatic treatment. Grade 3/4: stop treatment + aggressive symptomatic treatment. Consider desensitization.
Cabazitaxel[15,39,47,54-57]	Between <1% with concomitant prednisone and 6%.	Within minutes of the infusion, especially during the first and second infusions.	Flushing, rash, urticaria, dyspnea, drug-induced fever, bronchospasm with or without urticaria, allergy-related edema, angioedema, hypotension, erythema, anaphylaxis (in severe cases).	Antihistamines (diphenhydramine 25 mg or equivalent), corticosteroids (e.g. dexamethasone 8 mg or equivalent), or histamines (H_2)-receptor antagonist (e.g. ranitidine 50 mg or equivalent) at least 30 min before administration.	Supportive care measures, such as antihistamines, corticosteroids, i.v. fluids, oxygen, and bronchodilators.
Carboplatin[15,39,49,53,58-63]	8%-16% Incidence increases from 1% with ≤6 infusions to 27% with ≥7 infusions, to up to 46% with >15 infusions. Highest incidence with the eighth or ninth exposure.	Variable (minutes to hours). Risk increases with cumulative doses. Highest incidence at the eighth exposure. First IRR typically around the second and third re-exposure during the second line of therapy (eighth and ninth courses overall).	Nausea, vomiting, diarrhea, pruritus, urticaria, rash, erythema on palms and soles, abdominal cramps, facial edema, bronchospasm, wheezing, hypotension, tachycardia, dyspnea, chest pain, facial swelling, or anaphylaxis.	Corticosteroids and H1/H2 antagonists not routinely recommended. Can be considered in high-risk patients. Premedication may not prevent IRRs.	Grade 1/2: stop or slow the infusion rate + symptomatic treatment. Grade 3/4: stop treatment + aggressive symptomatic treatment. Consider desensitization.
Oxaliplatin[15,39,48,50,64-69]	7%-24% 0.5%-2% severe	Within 60 min (typically 5-10 min) after infusion start, but the first IRR can also occur throughout the treatment course. Incidence increases with the number of cycles; up to 20% after cycle 6.	Flushing, pruritus, urticaria, rash, palmar erythema, angioedema, hypertension, hypotension, sweating, watering, fever, dyspnea, back or chest pain, cough, throat tightness, nausea, diarrhea, laryngospasm, bronchospasm.	Corticosteroids and H1/H2 antagonists not routinely recommended. Can be considered in high-risk patients. Premedication may not prevent IRRs.	Grade 1/2: stop or slow the infusion rate + symptomatic treatment. Grade 3/4: stop treatment + aggressive symptomatic treatment. Consider desensitization. Administer treatment over 6 h.
Cisplatin[68,70-73]	5%-20% Incidence increases with the number of cycles and with concomitant radiation therapy. Higher incidence after cycle 6.	First IRR typically around the second and third re-exposure during the second line of therapy (eighth and ninth courses overall).	Urticaria, pruritus, respiratory distress, hypotension.	Adequate hydration and antiemetics to prevent nausea and vomiting.	Extravasation: stop the infusion immediately, aspirate any fluid collection, and administer sodium thiosulfate.

Continued

(Olsen et al., 2023)

Table 3. Continued

Drug	Incidence of IRRs	Onset of IRRs	Signs/symptoms of IRRs	Prophylaxis	Management
Procarbazine[30,39,53,74,75]	6%-18% Higher with concomitant use of anticonvulsants. 2% severe	Mostly in the first treatment courses.	Rash, urticaria, angioedema, toxic epidermal necrolysis, fever.	Steroid and diphenhydramine. Premedication with oral corticosteroids usually not successful once the IRR occurs, requiring treatment interruption.	Grade 1/2: symptomatic treatment. Grade 3/4: stop treatment + aggressive symptomatic treatment.
Nab-paclitaxel[15,30,39,48,49,53,76-78]	30% without premedication. 2%-4% severe anaphylactic reactions.	First or second dose, within the first 10 min of infusion. 1%-2% severe hypersensitivity reactions after an IRR despite adequate premedication.	Dyspnea, hypotension, tachycardia, flushing, skin reactions, bronchospasm, angioedema, urticaria.	No premedication with corticosteroids, prolonged infusions, or special i.v. infusion sets required. Limit the infusion to 30 min to reduce the likelihood of IRRs. One dose of i.v. dexamethasone + diphenhydramine (50 mg i.v.) and a H2 receptor antagonist (ranitidine 50 mg or cimetidine 300 mg i.v.) 30 min before the infusion.	Grade 1/2: stop or slow the infusion rate + symptomatic treatment. Grade 3/4: stop treatment + aggressive symptomatic treatment. Consider desensitization.
Asparaginase[15,53,79-81]	60% hypersensitivity reactions. 10% severe reactions.	Mostly within the first hour of infusion, with incidence and severity increasing with continued dosing.	Pruritus, rash, urticaria, abdominal pain, dyspnea, bronchospasm, laryngospasm, hypotension, angioedema.	Antihistamines and/or corticosteroids.	Grade 1/2: stop or slow the infusion rate + symptomatic treatment. Grade 3/4: stop treatment + aggressive symptomatic therapy switch to PEGasparaginase.
Anthracyclines[30,39,46,82]	Rarely cause IRRs and most reactions are mild. 7%-11% with PEGylated liposomal doxorubicin and daunorubicin.	Mostly in the first infusion.	Fever, flushing, chills, angioedema, rash, urticaria, pruritus, tachycardia, syncope, dyspnea, hypotension, nausea, vomiting, headache, and back and chest pain.	Not routinely recommended. Reduced infusion rate can be considered.	Grade 1/2: stop or slow the infusion rate + symptomatic treatment. Grade 3/4: stop treatment + aggressive symptomatic treatment. Consider desensitization.
Etoposide[30,39,53,83-87]	1%-3% anaphylactic-like reactions. Case reports described in the literature.		Chills, fever, tachycardia, bronchospasm, dyspnea, hypotension.	Corticosteroids and antihistamines. Slow the infusion over 30-60 min.	Grade 1/2: stop or slow the infusion rate + symptomatic treatment. Grade 3/4: stop treatment + aggressive symptomatic treatment. Consider desensitization.
Bleomycin[88]	1%	Immediate or delayed for several hours, usually after the first or second dose.	Fever, chills, mental confusion, hypotension, wheezing. Sudden onset of acute chest pain syndrome suggestive of pleuropericarditis during infusion.	$\leq$2 units for the first two doses in lymphoma patients, due to the possibility of anaphylactoid reactions. If no IRR, follow the regular dosage schedule.	Grade 1/2: stop or slow the infusion rate + symptomatic treatment. Grade 3/4: stop treatment + aggressive symptomatic treatment.

Continued

Table 3. Continued

Drug	Incidence of IRRs	Onset of IRRs	Signs/symptoms of IRRs	Prophylaxis	Management
Immunotherapy					
Pembrolizumab[131-135]	3% <1% grade ≥3 0.2% (of 2799 patients) severe or life-threatening (hypersensitivity, anaphylaxis).		Pyrexia, chills.	Antipyretics and antihistamines can be considered.	Grade 1/2: stop or slow the infusion rate with close monitoring + symptomatic treatment. Grade 3/4: stop and permanently discontinue treatment.
Nivolumab[136-140]	2%-5%, including grade 3/4. <1% grade 3/4 leading to treatment discontinuation.		Facial flushing, hives, angioedema.	Infusion time of 30 min safe. Premedication advised in case of grade 1/2 reactions. Antipyretics and antihistamines can be considered in case of a reaction.	Grade 1/2: stop or slow the infusion rate + symptomatic treatment. Grade 3/4: permanently stop the infusion + aggressive symptomatic treatment.
Ipilimumab[141-146]	0.6%-5.8%, mostly grade 2	More frequent with the second dose, suggesting that the first dose is a sensitizing one.	Cough, shortness of breath, chills, rigors, pruritus, maculopapular rash, facial flushing, chest, abdominal, and back pain.	Antipyretics and antihistamines can be considered. Patient observation for a short period of time after the infusion recommended to monitor the occurrence of IRRs.	Grade 1/2: stop or slow the infusion rate + symptomatic treatment (diphenhydramine and/or corticosteroids). Restart the infusion with close monitoring. Grade 3/4: stop the infusion + aggressive symptomatic treatment (including corticosteroids). Permanently discontinue treatment.
Durvalumab[147]	1.6% any grade 0.2% grade 3		Chills or shaking, itching or rash, flushing, shortness of breath or wheezing, dizziness, fever.	Premedication for prophylaxis of subsequent infusion reactions can be considered.	Grade 1/2: stop or slow the infusion rate. Grade 3/4: permanently discontinue treatment. Monitor patients for signs and symptoms of IRRs.
Atezolizumab[148-153]	1%-2% 1.3%-1.7% severe	Only reports of single cases: 10 min into the first infusion; after second lifetime exposure.	Dizziness, numbness, lack of consciousness, severe hypotension, chills, itching or rash, swelling of face or lips, flushing, shortness of breath, swelling, dyspnea or wheezing, fever, back or neck pain, anaphylaxis.	Antipyretics and antihistamines can be considered.	Grade 1/2: stop or slow the infusion rate + symptomatic treatment. Treatment may be resumed with close monitoring when the event is resolved. Grade 3/4: stop the infusion + aggressive symptomatic treatment. Permanently discontinue treatment.
Sintilimab[154,155]	2.3%-13% 0.8% grade ≥3 Pyrexia most frequent: 9% May cause severe or life-threatening IRRs, including severe hypersensitivity or anaphylactic reactions.	During or shortly after the infusion. Usually resolve completely within 24 h after completing the infusion. Pyrexia within 24 h of the first infusion, resolving on the same day and not reoccurring with subsequent infusions.	Infusion site pain and swelling, pyrexia, hypersensitivity, blood pressure increase, rash.		

5-HT3, 5-Hydroxytryptamine (serotonin) receptors; CRS, cytokine-release syndrome; IRR, infusion-related reaction; i.v., intravenous; NK1, Neurokinin 1 receptor.

What is Cytokine Release Syndrome (CRS)?

Cytokine release syndrome is caused by a large, rapid release of cytokines into the bloodstream. As the biotherapy agent interacts with its target, it releases cytokines that act as messengers, notifying other cells of the immune system to activate and join in the destruction of the target cells. In this manner, cytokines are responsible for coordinating a widespread, systemic response. The collection of symptoms that result from this release of an abundance of cytokines is known as Cytokine Release Syndrome (CRS). This reaction is especially notable with the first dose of monoclonal therapy when there are a large number of targets available for destruction. The reaction is less likely to occur with subsequent doses since most of the targets will have been destroyed by previous doses.

Signs and symptoms of cytokine release syndrome include:

- Fever
- Nausea
- Headache
- Rash
- Rapid heartbeat
- Low blood pressure
- Trouble breathing

CRS causes inflammation throughout the body and can cause significant organ damage. This condition may occur after treatment with biotherapy, such as monoclonal antibodies and CAR-T cells (see Table 4).

Cytokine release syndrome is usually associated with the first infusion and does not necessitate the discontinuance of the treatment. This reaction usually occurs within 30 minutes to 2 hours after the infusion. For mild or moderate infusion-related reactions, the reaction resolves by slowing or stopping the infusion and providing supportive care to resolve symptoms. Often, the infusion can be resumed after symptoms resolve at a slower rate per hour for the remainder of the infusion. Most patients have a mild reaction, but severe or life-threatening reactions may occur.

Table 4: Biotherapy Drugs Associated with Hypersensitivity Reactions and Cytokine Release Syndromes

• Interferons • Aldesleukin • Temsirolimus • Blinatumomab • Tisanglecleucel (CAR-T) • Brentuximab • Rituximab	• Alemtuzumab • Bevacizumab • Gemtuzumab ozogamicin • Trastuzumab • Ipilimumab • Ofatumumab
(Povlich, et.al, 2014)	

Prophylaxis and Pre-medications

Nurses that administer chemotherapy and biotherapy need a broad understanding of the drugs that may have the potential to cause an infusion-related reaction. Obtaining baseline information about the patient and the drug prior to the infusion can provide insight as to what kind of reaction may occur. Baseline information about the patient includes allergy history (drugs, blood products, foods), prior exposure to the agent to be given, past medical history of asthma/eczema/allergic conditions. Other factors that may contribute to the risk for infusion-related reaction include age, concomitant diseases, concomitant medications that may be contraindicated, tumor burden.

Baseline information about the agent to be administered includes the potential for that drug to cause an infusion-related reaction (see Tables 3 and 4). All chemotherapy and biotherapy agents have the potential for reaction; however, certain drugs are known to have a higher risk for reactions such as: asparaginase, cisplatin, paclitaxel, and rituximab. The risk for hypersensitivity to carboplatin increases after the sixth infusion.

Pre-medications may be given prior to administering medications associated with allergic reactions or anaphylaxis. Premeditations often include H2 antagonists (diphenhydramine), H1 antagonists (famotidine or ranitidine), anti-inflammatory agents (acetaminophen, and/or corticosteroids). Pre-medications may be given as standard of care with medications commonly associated with allergic reactions and anaphylaxis or may be given as the result of previous reactions.

When administering drugs with high potential for anaphylactic reactions, the nurse should be prepared for quick response to symptoms of anaphylaxis: know the patient's weight and what the expected doses of diphenhydramine, hydrocortisone, and epinephrine would be for the patient. It is much easier to have this information readily available, rather than have to spend precious seconds calculating doses during an acute reaction.

Infusion-Related Reaction Management

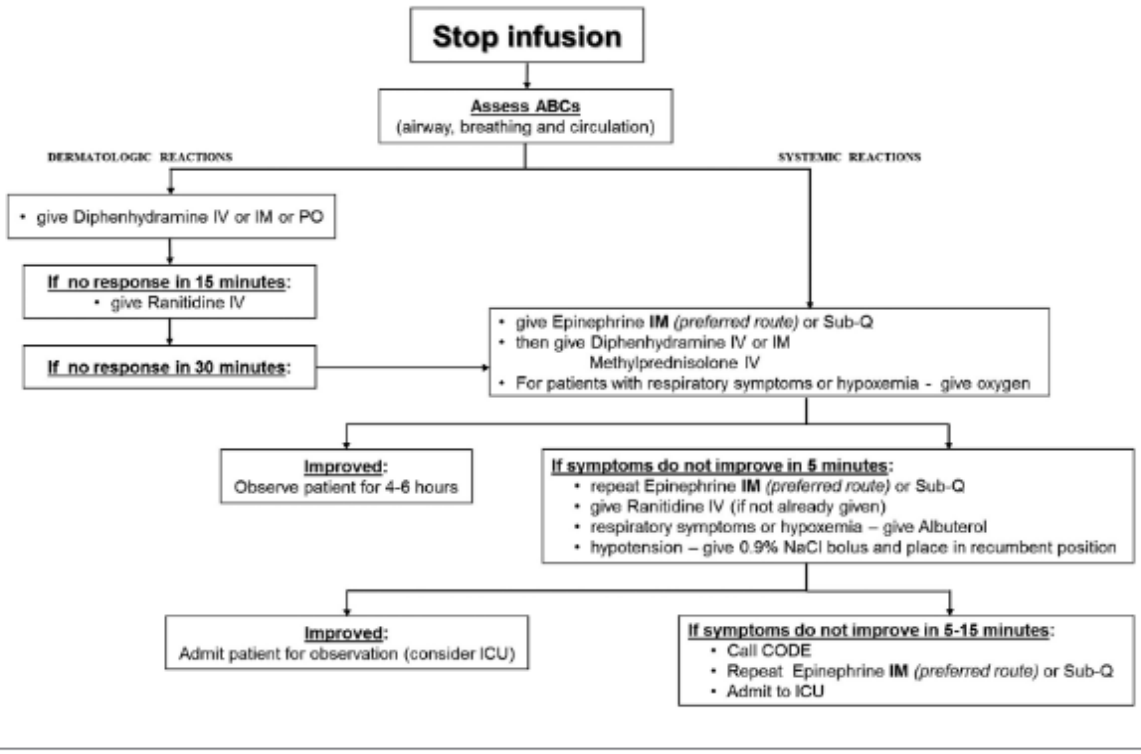
Infusion-related reactions, whether antibody-mediated or non-antibody mediated, require immediate nursing management at the onset of any signs or symptoms. The FIRST action is to STOP the infusion and assess the patient's airway, breathing, and circulation. The nurse should stay with the patient and call for help. These reactions can occur quickly, and symptoms can progress rapidly, so the patient should never be left alone. The course of care is dependent on the findings. Figure 1 shows an algorithm for the management of allergic reactions.

Medical management of infusion-related reactions is based on severity of symptoms. Mild to moderate allergic reactions, with symptoms limited to dermatologic findings (rash, urticaria, pruritis) can be managed with antihistamines and anti-inflammatory medications given orally, intramuscular or intravenous injections. For mild to moderate CRS, slowing the infusion rate may be enough to control symptoms.

For infusion-related reactions that are more severe, involving cardiopulmonary symptoms, initial medical management the same for both antibody-mediated and non-antibody mediated reactions: prompt intravenous administration of antihistamines and anti-inflammatory medications. Epinephrine should also be given as soon as possible if the patient demonstrates angioedema, bronchospasm, or respiratory distress.

Some institutions keep anaphylaxis kits available at bedside or provide computerized order sets for anaphylaxis medication orders prepared in advance to allow for quick response to concerning symptoms.

Figure 7.12. Algorithm for Management of Allergic Reactions



Note. ICU = intensive care unit; IM = intramuscular; IV = intravenous; PO = *per os* (by mouth); SubQ = subcutaneous.
Courtesy of Ann & Robert H. Lurie Children's Hospital of Chicago.
DISCLAIMER: This diagram was developed solely for the use of Children's Hospital of Chicago Medical Center and its affiliates ("Medical Center"). The information contained herein shall not be relied upon by individuals or entities outside Medical Center for accuracy, timeliness, or any other purpose.

Documentation is essential with reaction management. Accurate documentation can help guide decisions regarding the safety of future administration of the drug. In order to maintain a consistent method of describing and classifying allergic reactions, The National Cancer Institute has created a Common Terminology for Adverse Events (CTCAE) provides grading criteria for allergic reactions (see Table 5)

Table 5: National Cancer Institute Grading Criteria for Allergic Reactions, Anaphylaxis, and Cytokine Release Syndrome

Table 7.7. National Cancer Institute Grading Criteria for Allergic and Anaphylactic Reactions and Cytokine Release Syndrome

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Allergic reaction (a disorder characterized by an adverse local or general response from exposure to an allergen) Note: if the reaction is related to an infusion, use the section "injury, poisoning and procedural complications: Infusion related reaction."	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Anaphylaxis (a disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death)	—	—	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema or angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Cytokine release syndrome (a disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, or hypoxia caused by the release of cytokines)	Fever, with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to less than 40% O_2	Hypotension managed with one pressor; hypoxia requiring more than 40% O_2	Life-threatening consequences; urgent intervention indicated	Death
Infusion related reaction (a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances)	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated, but the patient responds promptly to treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications are indicated for at least 24 hr.	Prolonged reaction (e.g., not rapidly responsive to symptomatic medication or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention required	Death

Note. IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs.
From *Common Terminology Criteria for Adverse Events* (v. 5.0), by the National Cancer Institute, 2017.
Retrieved from https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

Adapted from NCI CTCAE version 5.0

Desensitization

Patients who have experienced Grade 3 or 4 allergic or anaphylactic reactions may still need to continue the medication in order to complete treatment. Desensitization may be implemented for the patient to tolerate the infusion safely. Desensitization often occurs in intensive care units, with allergy/immunology as a consulting service. Patients may be pre-medicated several hours to several days prior to the infusion. The medication is often diluted and given at a slower rate over several hours to allow the patient's body to adjust to the drug, in order to tolerate future infusions.

Follow up/Patient and Family Education

Although most reactions occur within the first 30 minutes of drug administration, a delayed reaction, occurring hours to days later, may occur. It is essential to educate patients and families on the signs and symptoms of delayed reactions which could include rashes, urticaria, respiratory symptoms (cough, wheezing, respiratory distress). Families should be aware of what interventions that they can do immediately at home along with instructions about who to call. This information should be thoroughly explained to the patient with teach back verification, as well as written instructions.

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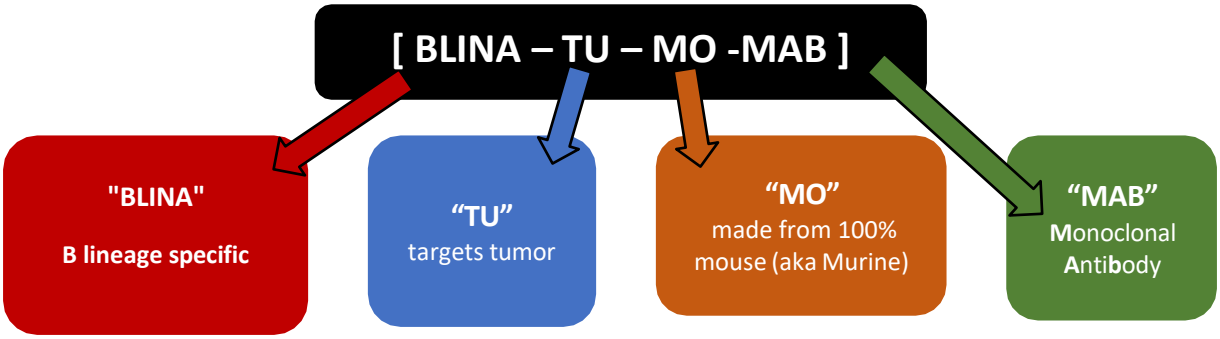
BLINATUMOMAB



By Karen Kestenbaum, DNP, APN, CPHON and Shelly Tolley, MSN, RN, CPHON

Learner Outcomes:

1. Identify blinatumomab’s mechanism of action and immunotherapy classification.
2. Recognize the nursing considerations for blinatumomab administration and special considerations.
3. Identify the appropriate use of blinatumomab and future applications of the drug

Please note the use of blinatumomab is ever evolving. The information is current as of August 16, 2024

Blinatumomab Fun Facts:

1. Blinatumomab is produced in Chinese hamster ovarian cells (Amgen, 2024)
2. Blinatumomab received its international non-proprietary name from the World Health Organization; the name is derived from the term ***B-lin***eage specific ***a***nti-***tu***mor ***mo***use ***m***onoclonal ***a***nti***b***ody (Nagorsen et al., 2012)
3. Blinatumomab entered its first human study in 2001 (Nagorsen et al., 2012)

Definitions:

Antibodies are molecules that can recognize and attach to a foreign substance or harmful cells in a person’s blood or tissue. A monoclonal antibody is an antibody that has been reproduced in a laboratory from a specific type of plasma B cell that will bind to a specific marker. Monoclonal antibodies can be used to bind with receptors on cancer cells to provide targeted immunotherapy (Nelson et al., 2000).

Clusters of differentiation (CD) are the names given to cell surface molecules that are used to differentiate between cells. CD markers on the surface of cells are expressed in response to changes in the environment or changes in the cell. Abnormal CD markers, identified by flow cytometry in the blood and bone marrow, are one of the ways used to diagnose leukemia (Shahrabi et al., 2020).

Introduction:

In the past, chemotherapy alone has been the main treatment for patients with B-cell acute lymphoblastic leukemia (ALL). Patients who were unable to achieve remission or who relapsed have had to undergo

hematopoietic cell transplant (HCT). Despite best efforts, there are some patients with B-cell ALL who have a poor prognosis, are unable to achieve remission, or relapse. With the development of blinatumomab, which is a monoclonal antibody that targets CD19 and CD3, there is some hope for some patients with an otherwise dismal prognosis (Nagorsen et al., 2012).

History of Cancer Immunotherapy:

Immunotherapy is a type of treatment where a person's own immune system is used to fight their cancer (Dede et al., 2023). Cancer immunotherapy can be described as either passive or active. Passive immunotherapy is when cancer agents are used to augment tumor response. Examples of these agents are cytokines and monoclonal antibodies. Active immunotherapy is when agents are used to modulate or activate the immune system. An example of these agents are vaccines (Dede et al., 2023).

In 1975, hybridomas and monoclonal antibodies were developed, and changed the treatment options for cancer. This introduced the idea of treating cancer individually by targeting mechanisms (DeVita & Rosenberg, 2012). Over the past four decades, advancements in immunotherapy have focused on achieving the best immune response with the smallest amount of side effects (Dede et al., 2023)

Monoclonal antibodies are one of the most rapidly evolving types of immunotherapy. The development of monoclonal antibodies has led to the overall improvement in survival rates of cancer (Dede et al., 2023)

Blinatumomab Patient Population and Purposes

Blinatumomab is now approved by the United States Food and Drug Administration (FDA) for the treatment of pediatric patients that have CD19 positive B-cell ALL in consolidation phase and for those who have evidence of minimal residual disease (MRD), relapsed or refractory disease (FDA, 2024).

Results of Children's Oncology Group (COG) AALL1331 demonstrated that using blinatumomab in patients with low, intermediate, and high-risk relapsed leukemia improved overall survival. Additionally, the drug was well tolerated and had less toxicity in comparison to conventional chemotherapy (Hogan et al., 2023).

On June 14, 2024, the FDA approved the use of blinatumomab as consolidation therapy for CD-19 positive Philadelphia chromosome negative B-cell ALL. This approval was based on results of trials that revealed that patients receiving blinatumomab and intensive chemotherapy had superior overall survival in comparison to patients who received only intensive chemotherapy (FDA, 2024). This change in indication stemmed from a phase 3 trial which looked at outcomes and overall survival of MRD negative, Philadelphia chromosome negative adult patients who received standard consolidation chemotherapy versus standard consolidation chemotherapy with the addition of blinatumomab (Litzow et al., 2024). Results indicated that the addition of blinatumomab to consolidation chemotherapy significantly improved rate of overall survival (Litzow et al., 2024). Due to these exciting results, upfront chemotherapy regimens have now changed to include the use of Blinatumomab in MRD negative, CD19 positive B-cell ALL patients.

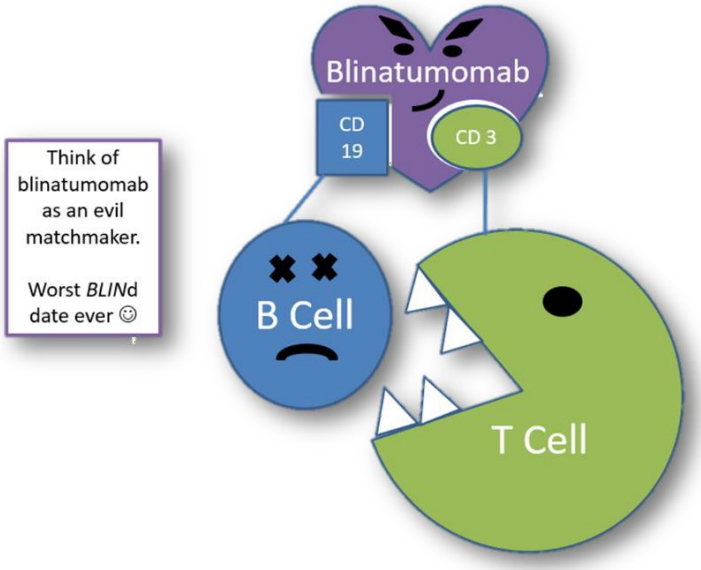
Mechanism of Action/Pharmacodynamics (Including Receptor Identification)

In the body, T-cells regulate all activities of cells in immune responses (Heimall, 2023). By doing so, the T-cell receptor-CD3 complex carries the signal across the T-cell receptor, which in turn dictates the T-cell activation by antigen-presenting cells and target cell recognition. The T-cells activate the immune response to dispose of foreign bodies and unusual cells within the body (Heimall, 2023).

Blinatumomab is a Bi-Specific T-Cell Engager (BiTE). The words "Bi-specific" indicate that blinatumomab attaches to two separate receptors: CD19 and CD3. CD19 is found on the surface of B-cells and CD3 is found on

the surface of T-cells. Blinatumomab connects CD3 on the T-cells receptor and engages it (hence the name T-cell engager)[OBJ]This attachment then forms and initiates the subsequent cytolytic action between T-cells and B-cells (both malignant and benign). This process leads to lysis of CD-19 positive cells (B-Cells) (Amgen, 2024). Blinatumomab is merely initiating contact between foreign antigens and T-cell receptors to begin the disposal process. It sounds like the "worst BLIN'd date ever"! (See Figure 1).

Figure 1. Mechanism of Action for Blinatumomab and other BiTe engagers



Picture courtesy of Caroline Anderson, Cook Children's Medical Center, Fort Worth, TX.
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Adverse Effects

Almost all (98.5%) patients that receive blinatumomab will have an adverse drug reaction. Approximately 60% of those adverse reactions are serious ones. The two most significant adverse events are cytokine release syndrome (CRS) and neurotoxicity (Mirfakhraie et al., 2022).

Cytokine release syndrome occurs when cytotoxic T-cells are activated causing release of inflammatory cytokines resulting in a systemic inflammatory response wherein interferon gamma, interleukin 6 (IL-6), and interleukin 10 (IL-10) are elevated (Mirfakhraie et al., 2022). The typical time of onset of CRS is two days from the start of the infusion and resolves by day 5 of the infusion. Signs/symptoms of CRS include fever, headaches, nausea, hypotension, transaminitis, increased bilirubin, and disseminated intravascular coagulation (DIC). These symptoms may overlap with those of capillary leak syndrome and macrophage activation syndrome. This can happen in approximately 15% of patients with relapsed/refractory ALL and in 7% of those with positive MRD. In severe or life-threatening situations, blinatumomab may be discontinued permanently (Amgen, 2024). Patients with higher disease burden are at increased risk for CRS. Prior to starting blinatumomab, healthcare providers consider risk for CRS and may give dexamethasone prior or reduce the dosage to improve tolerability. Although corticosteroids have been shown to be beneficial with CRS, there is concern whether they reduce the efficacy of

blinatumomab as they interrupt the function of T-cells. Consideration of the use of tocilizumab, an IL-6 blocker, can be helpful in reducing the symptoms of CRS, as it does not interrupt the function of T-cells. Dosage of tocilizumab is for patients less than 30kg is 12mg/kg and for those ≥ 30 kg 8mg/kg (max dose 800mg) (Mirfakhraei et al., 2022).

Approximately 65% of patients that receive blinatumomab have had neurological toxic events in clinical trials (Amgen, 2024). Typical symptoms of neurological toxicity include headaches and tremors. Grade 3 or higher neurological events occurred in approximately 13% of patients in clinical trials. These signs/symptoms include encephalopathy, seizures, aphasia, confusion, disorientation, and coordination and balance disturbances (Amgen, 2024). Blinatumomab neurotoxicity is thought to be due to the release of cytokines. For grade 1 or 2 neurotoxicity, it is recommended to use supportive care with intravenous fluids, anti-inflammatory agents, and respiratory support if needed. Steroid initiation can be considered to avoid symptom progression. For grade 3 neurotoxicity, stop blinatumomab and allow symptoms to resolve to grade ≤ 1 for 3 days prior to resumption of the medication. Dose reduction for 7 days can be considered after resumption of blinatumomab. If neurotoxicity symptoms persist beyond 7 days or for grade 4 neurotoxicity, blinatumomab may be permanently discontinued (Mirfakhraie et al., 2022).

Other adverse events that have been associated with the administration of blinatumomab include: tumor lysis syndrome, elevated liver enzymes, fever, neutropenia, pancreatitis, infections, and leukoencephalopathy (Amgen, 2023).

Administration of Blinatumomab

Blinatumomab is administered as a continuous IV infusion at a very slow rate for 28 days per cycle. Due to side effects, hospitalization is recommended for the first three days of the first cycle and for the first two days of the second cycle (Lexicomp, 2024). It is recommended that blinatumomab is infused through a central line (Bernhardt et al., 2021). Interruptions should be kept at a minimum and consider readmission to the hospital for monitoring for prolonged interruptions of greater than four hours. The IV tubing should only be primed with the drug and not primed with normal saline. This allows the drug to reach the patient immediately. Supplies should be polyolefin, DEHP-free PVC or ethyl vinyl acetate. (Lexicomp, 2024). Blinatumomab typically runs at a rate of 5 ml/hr (can be lower rates for large volume bags). Infusion bags can last for 24, 48, 72, 96 hours or seven days, depending on institutional policy. Currently, patients who are above 1500 grams and are not neonates, are now able to receive bags lasting for seven days. Filters of 0.2 micron are used on bags but should not be placed on seven-day bags to avoid blood backup. In-line filters should not be used with 7-day bags (Amgen, 2024).

Blinatumomab infusion bags are prepared with overfill of the medication to account for the IV line when priming (Amgen, 2024). Tubing of blinatumomab infusions should be secured with an engineered securing device to minimize risk of disconnections during infusions (Bernhardt et al., 2021).

Nursing considerations

For blinatumomab, there are no exposure guidelines established by the National Institute for Occupational Safety and Health (NIOSH) and Occupational Safety and Health Administration (OSHA) (SDS, 2022). Proper personal protective equipment (PPE) should be based on institutional guidelines.

Every attempt should be made to minimize blinatumomab infusion interruptions. Unavoidable interruptions may occur, such as for blood draw, medication administration, implanted port needle changes, or for sedation for procedures. Length of the interruption should be lessened in duration as much as possible (Bernhardt et al., 2021). Facilities may choose to place a peripheral IV to minimize interruptions for these situations (Withycombe et al., 2023). Many institutions have created a log to track interruptions to determine if the cumulative interruptions are significant enough to add additional time to the end of the blinatumomab cycle (Bernhardt et al., 2021).

It is discouraged to flush an IV line with blinatumomab infusing. Flushing an IV line that contains blinatumomab can lead to a bolus of blinatumomab (Bernhard et al., 2021). For example, if a nurse was to use a 10 mL flush to clear the line for lab draws, it is possible to flush 10 mL worth of drug through the line at once. This would cause an increased risk for side effects, since the drug would have been infused in less than 5 minutes, instead of over 2 hours. Additionally, for this reason, it is not necessary to confirm blood return daily. Institutional policy will guide flushing practices (Bernhardt et al., 2021).

There has been much discussion regarding optimal nurse to patient ratio for patients that are receiving blinatumomab. Although nurse to patient ratios are typically lower during the first 72 hours of infusion (Withycombe at al. 2023), there is no evidence to support the ideal ratio (Bernhard et al., 2021). Additionally, there are no standard recommendations regarding frequency of vital signs or patient assessments for those patients who have blinatumomab infusing (Bernhardt et al., 2021).

Blinatumomab must be infused with a programmable, non-elastomeric pump, that can be locked. Some institutions may use the same pump for both inpatient and outpatient to allow for easy transition between settings. Unfortunately, since the rate of infusion is so low, the use of inpatient pumps may result in blood backing up into the line. If blood backs up to the line, normal saline may be added to the blinatumomab line to keep the blood from backing up (Bernhardt et al., 2021). Helpful precautions that can be used to minimize variance of infusion rate when administering blinatumomab in the outpatient setting include maintaining infusion pump at the same level of the patient, keeping infusion bag at room temperature, and consideration of avoiding the use of extra infusion connectors such as closed system transfer devices (Bernhardt et al., 2021).

Prior to a patient being discharged home with blinatumomab, it is essential that the patient/caregiver is provided with the necessary education for successful outpatient administration. Patients/caregivers should be educated on signs/symptoms of adverse reactions, caring for the central line, when to call the healthcare team, and infusion pump trouble shooting (Bernhardt et al., 2021).

Special Patient Population Considerations:

Blinatumomab may cause fetal harm in a pregnant woman. For this reason, it is important to verify the pregnancy status in those patients of childbearing potential prior to initiation of the drug. Female patients are cautioned to use effective contraception while receiving blinatumomab and for 48 hours after discontinuation of the drug (Amgen, 2024).

Children with Trisomy 21, that are over ten years of age, appear to have an increased risk for seizures when receiving Blinatumomab. The majority of seizures occurred during the first three days of infusion. Due to the increased risk for seizures, it is advisable that patients with Trisomy 21 receive seizure prophylaxis when receiving blinatumomab, especially if they are ten years of age or older. It remains uncertain why these patients have a predisposition to seizures (Li et al., 2021).

Vaccination with live viruses is not recommended for 2 weeks before receiving blinatumomab, during infusion and until immune system recovers (Amgen, 2024).

The Future of Blinatumomab

Despite **cure rates** of 90% for children with ALL using standard chemotherapy, there is an increasing awareness of the acute and long-term toxicities of conventional chemotherapy. Furthermore, there are a portion of children that cannot tolerate their treatment due to toxicities (Hodder et al., 2023). Additionally, patients with Trisomy 21, have a high incidence of chemotherapy related adverse effects. In these patients, blinatumomab can be used upfront to minimize these complications and improve outcomes (Queudeville & Ebinger, 2021).

Recent studies have shown the benefits of the use of blinatumomab with upfront chemotherapy in patients with unfavorable cytogenetics (Queudeville & Ebinger, 2021). KMT2A-rearranged infant ALL historically has had a three-

year event free survival rate below 40% (Van ser Sluis et al., 2023). Despite intensifying chemotherapy, outcomes have not improved. A recent study added blinatumomab to backbone chemotherapy. Results indicated that the administration of blinatumomab was safe in infants, increased complete MRD response, and had improved short-term survival (Van der Sluis et al., 2023). These results are promising for patients who have had a historically very poor prognosis.

Other studies are exploring the use of blinatumomab in patients with Philadelphia positive ALL (Mirkfakhraei et al., 2023). Blinatumomab has been shown to be effective in adult patients with relapsed/refractory Philadelphia positive B-cell ALL (Martinelli et al., 2021). This study is paving the way for treatment of Philadelphia positive B-Cell ALL patients with blinatumomab.

There is some concern that patients may become resistant to blinatumomab due to decrease in T- cell activity or loss of the CD19 target. Studies are beginning to explore the addition of immune checkpoint inhibitors, such as nivolumab and ipilimumab, which can help improve T-cell function and overcome drug resistance. (Mirfakhraie et al., 2023).

Although, the addition of blinatumomab to certain pediatric ALL patient populations has been shown to be beneficial, there are questions that remain: how many cycles of blinatumomab are needed, why do some patients respond to it while others do not, when is the appropriate time point to introduce a cycle of blinatumomab, and finally in those who are relapsed, is it able to induce a long lasting remission, decreasing the need for hematopoietic cell transplant in some patients (Queudeville & Ebinger, 2021)?

Conclusion

With the advancement of immunotherapy, where a patient's own immune system attacks the cancer, treatments are becoming more individualized and personalized. Monoclonal antibodies, like blinatumomab, are an example of a type of immunotherapy. Since monoclonal antibodies are more targeted, they often have less cytotoxicity (Dede at al., 2023). Blinatumomab is a drug that has improved outcomes in those patients with CD19 B-cell ALL leukemia and has given hope to children that otherwise would not have any.

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We are Research Nurses: A Research Review

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Learner Outcomes:

1. Identify the purpose of research in Pediatric Hematology/Oncology.
2. State basic research processes, terms, and concepts.
3. Recognize "adverse events" and how they apply to research studies.
4. Identify their own role in pediatric hematology/oncology research.
5. Apply research understanding to a case study.

Introduction

Over years, decades, and even centuries, cancer treatment has changed, improved, and progressed. Initially, separate treatments were instigated to treat specific diseases, such as surgery to treat abdominal or breast cancers or radiation to treat skin carcinomas (American Cancer Society, 2014a & 2014b; National Cancer Institute, 2020). These treatment methods were commonly used, especially towards the end of the 19th century and beginning of the 20th century. Then, around World War II, chemotherapy was developed after observations from nitrogen mustard exposure and from antimetabolite production (American Cancer Society, 2014c; National Cancer Institute, 2020). During that time of development, agents such as aminopterin forged a path for the development of the more commonly known chemotherapy methotrexate (American Cancer Society, 2014c). The creation of chemotherapy progressed to the use of multi-modal treatments and concomitant therapies (American Cancer Society, 2014c). By combining chemotherapies to treat one disease known as concomitant therapy, or by combining multiple modes of therapy into a treatment regimen (also known as multi-modal therapy), cancer cure rates improved dramatically. Cancer diagnoses became treatable and curable due to this generation of development.

However, certain diseases still laid untouched and incurable, despite the incredible therapeutic improvements. This led to the evolution of two ideas. First, cancer diagnoses are detectable to a genetic and molecular level. And second, by identifying diagnoses so minutely, cancer can receive targeted care per diagnosis (National Cancer Institute, 2022; Philips, 2020). Therefore, now both current oncologic and hematologic research integrates these ideas by developing treatments with upgraded technology, such as relying on vectors to transfer cell-altering medications or slicing and dicing genetic code to improve the gaps of individual genetics (American Cancer Society, 2014d & 2014e; U.S. Food & Drug Administration, 2023). These developments came from continued research. Current treatments used to treat and cure our pediatric hematologic and oncologic patients are remarkable. As seen throughout

history, research aids in the development, treatment, and cures of multiple diseases affecting this patient population.

Many outcomes and cures over the last 50 years have been forged through ongoing research. However, for pediatric hematology/oncology nurses, research is not in the forefront of their minds. The role of the bedside nurse is to assess patients, draw ordered labs, give treatment and supportive cares, document, and provide care extensively and holistically for each patient. As nurses, our daily process is to *eat, sleep, crush cancer, and repeat* on a daily process. But it is because of nurses that research thrives. Not only do nurses provide wonderful care based on previously proven effective treatments, but it is the cares, treatments, and documentation of bedside nurses that provided the proof of these successful treatments that have led to increased cure rates for childhood cancers and blood disorders. Nurses, now, are contributing to future patients by continuing the research cycle by proving that currently investigated treatments and medications are optimal for future patients. As pediatric hematology and oncology nurses, we are all research nurses for we are all contributing to our future, while welcoming the achievements of the past.

Therefore, a research review is paramount for APHON Chemotherapy/Biotherapy provider nurses. This is a straightforward review of the basics of research, as it applies to pediatric hematology/oncology patient population. As part of this review, we will review terms, processes, and applicable know-hows.

To start, research terms to know:

- **Consortium:** This is an entity or an established group of researchers that conduct research. For example, the Children's Oncology Group (COG) is a research consortium.
- **Participants:** These are individuals who are being researched and are participating in a research study (Herring et al., 2019, p. 40). They can also be referred to as subjects, and examples of participants include pediatric hematology or oncology patients.
- **Principle Investigator (PI):** The individual who takes responsibility and management for all research conducted and data collected at an individual site or for an entire research study. Responsibilities can be delegated, but PIs are responsible for all final decisions and outcomes submitted to the consortium (National Cancer Institute, 2024).
- **Clinical Research Coordinator (CRC):** This is a healthcare professional that "coordinates daily clinical trial activities and plays a critical role in the conduct of the study" (Washington University in St. Louis, 2007). Tasks may include patient enrollment,

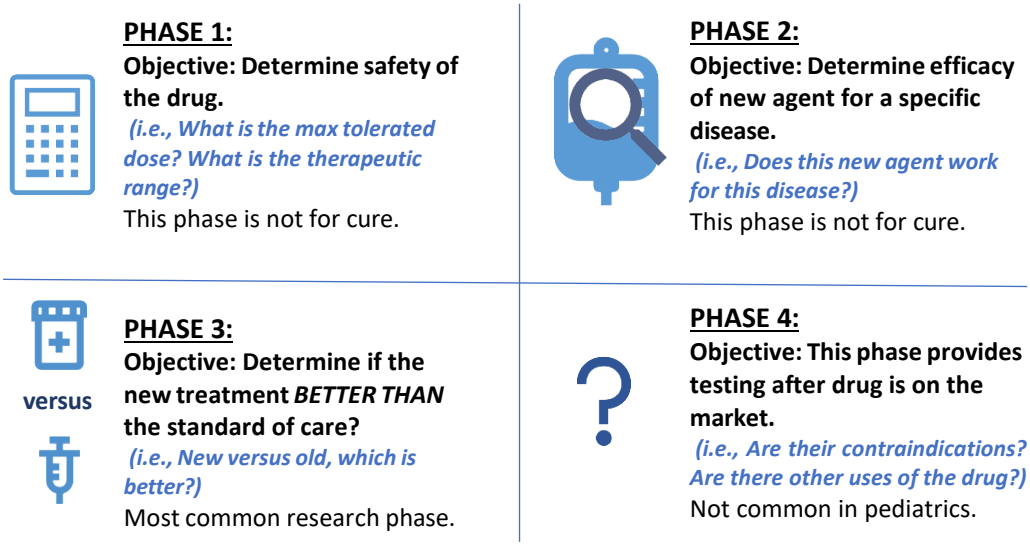
updates, patient communications, data submission, and collecting and/or sending out study specimens, only to name a few. Sometimes, these clinical research coordinators fall under the term "data manager" as well, determined by institutional policy and practice (National Cancer Institute, 2024).

- **Pediatric Hematology/Oncology (Clinical) Research Nurse:** This is a nurse who has similar responsibilities to a CRC but often rely on their experiential background necessary for specific data interpretation and clinical discernment essential for study compliance and data submission. Sometimes this role is also identified as a "data manager" and then other research nurses are to help "take care of patient[s] during a clinical trial" (National Cancer Institute, 2024). The term can be interchangeable based on institutional policy and practice.
- **Good Clinical Practice (GCP):** This is a national quality standard used to direct research through "design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinic trials" (Vijayananthan & Nawawi, 2008). It determines effective and correct documentation, reporting and recording processes.
- **Regulatory Agency:** A group or body of people that uphold standards of research, such as an institutional review board (IRB; Herring et al., 2019, p. 48). Research studies are obligated to follow the guidance of the IRB, linked with their consortium or institution.
- **Pharmacokinetic labs (PK labs):** Pharmacokinetics refers to the study of how a drug moves through the body, through ingestion, process, metabolize, and elimination (Herring et al., 2019, p. 23-25). PK labs are used to assess this movement throughout the body, and therefore there are usually multiple PK labs drawn for a study's initial drug dose.

Research Design Review

There are two common types of research used for childhood cancers. One classification is the "biological" or "repository" style of research, which collects data and studies it to the genetic and molecular level. The other classification is known as "therapeutic" research studies. The therapeutic research studies are designed with the four phases of research, or Phase I, II, III, or IV (see Figure 1; Herring et al., 2019, p. 47-48). According to the Children's Oncology Group (COG, a leader in childhood cancer trials), the classifications of "trials include front-line treatment for many types of childhood cancers, studies aimed at determining the underlying biology of these diseases, and trials involving new and emerging treatments, supportive care, and survivorship" (COG, 2023). Advances in childhood cancer

come from validated timely research. For example, 50 years ago, leukemia was viewed as almost incurable, but now more than 90% of childhood cancer patients are cured (Sharpless, 2021). But there are still gaps in care for some childhood cancers, including soft tissue and central nervous system cancers (Sharpless, 2021). Therefore, research aims to provide a change for these lagging cure rates.



(Fig. 1, The four phases of research. *Created by Shelly Tolley.*)

Besides COG, consortiums are typically created to focus as disease-based centers, such as the Pacific Pediatric Neuro-Oncology Consortium (PNOC) focusing on treating neuro-oncology tumors, or the North American Consortium for Histiocytosis (NACHO) focusing on treating histiocytic diseases including Langerhans Cell Histiocytosis (PNOC, n.d.; NACHO, 2015). These are only a few examples of the current expansion within childhood hematology and oncology. Through these consortiums, they aim to breach the gaps to improve cure rates. As research progresses and areas are explored, such as biotherapies/immunotherapies, combining drugs/treatments, making genetic alterations, and supporting patients with adverse side effects, the future of childhood cancer has potential.

Nursing Considerations

Understand the Study and the Treatment

Before caring for a patient, a hematology/oncology nurse should understand the study and its treatment, specifically learning the *why* behind the protocol and its treatments. For example, nurses can learn why this patient was chosen to receive this treatment. Or why does this treatment work on this patient? By learning the reason behind the study and the treatment, a caregiver can understand the importance of the documentation, study specimens, and treatment processes. That understanding can

ensure accuracy in protocol adherence and study specimen collections, and better outcomes for current and future patients. After understanding the reasoning, learn the requirements for this patient and this study.

Understanding the Study's Nursing Actions

Labs

Study requirements can include collecting or sending specimens. Bedside caregivers and study staff collect specimen data for multiple reasons. Also, these specimens can be identified as observations and they can include blood, tissue, stool, saliva, bone marrow, and cerebral spinal fluid, to name a few. To understand the different types of study observations, here is an observations review:

- **Pre-study specimens for genetic or molecular identification:** These specimens contribute to the biological or "repository" studies that serve two purposes. One, the specimens contribute to future science enabling identification of common genetic and molecular patterns linked to specific diseases or diagnoses. Second, these specimens identify what specific genetic markers that each patient possesses, and therefore dictate treatment modalities or treatment pathways. A common repository available through COG is known as the "Project Every Child" study or APEC14B1, or there is a different comprehensive molecular characterization study known as the TARGET study which extends beyond, but includes researchers from COG (Philips, 2022).
- **Initial/baseline study observations:** These specimens offer baseline patient assessments, and it is important that these specimens are drawn ***prior to ANY*** treatment, as specified by the protocol, including drawing any labs, taking any medications, and completing any quality-of-life questionnaires. Once consents are completed, then baseline observations may be completed according to protocol guidelines. Baseline assessments completed after treatment has begun can disqualify a patient from a study, and therefore the patient can miss out on new life-saving treatment.
- **Treatment study observations:** These specimens are taken throughout treatment. Some of these specimens could be Pharmacokinetic labs (PK labs). PK labs are the labs that identify how a drug is absorbed, metabolized, used, and excreted through the body or in other words, how the drug moves through the body (Herring et al., 2019; Tantisira & Weiss, 2024). PK labs are common among Phase 1 and 2 study designs but can be used throughout any study. Per protocol specifications, it is important to obtain these specimens **ON TIME,** as the results can dictate how much drug the patient will receive next or identify the efficacy of the drug currently

in the patient. These specimens are often sent out to specialty labs throughout the country, and even the world, for processing.

- **Standard of care observations:** These are specimens often determined by each institution and tend to be handled through the institution's normal specimen processing system. With that in mind, a protocol often still requires certain observations as part of standard care. It is most important that these observations are completed to maintain study compliance, and to obtain them within the specified protocol timeframe.
- **End of treatment observations:** As a patient's treatment comes to an end and they are removed from a treatment study, there are observations that need to be performed (i.e., labs collected, or measurements taken) to identify each patient's response to the study. Obtaining these end of treatment observations is as important as obtaining any other specimens and must be collected within the timeframes specified by the protocol.
- **Follow-up observations:** Although patients no longer receive treatment, they are often followed by the study for an extended period, the average follow-up timeframe being for 10 years after a patient enrolls on a study. Most studies, especially phase three studies, have overarching aims to improve survival rates in patients. By following patients long-term and obtaining that data at designated timepoints, survival rates and study effectiveness can be determined. Therefore, these specimens must be obtained, and they often have a date range that is appropriate for specimen collection.
- **Optional observations:** The term "optional" is a deceptive term in the context of specimen collection. The term "optional" refers to the patient's ability to choose to contribute to certain non-obligatory parts of a study. The patient determines ***at the time of enrollment***, when they sign the study consent, whether they will participate in these optional studies, or not. If the patient chooses to participate in optional studies, then the caregivers are obligated to obtain those "optional" observations, to the best of their ability.

Observations besides labs

Lab specimens are important, but sometimes studies ask for additional observational data such as an abdominal girth measurement, head circumference, height and weight, body surface area, or even activity level identified through play scales such as the Lansky Play Scale or the Karnofsky Performance Status Scale. Each of these elements are requested by the study or protocol for a reason. Just like any lab specimen, when looking at these additional observational elements there are three principles to remember: 1) right observation, 2) right timing, and 3) right process. For example, the

protocol might state an abdominal girth is required on Day 1 of Cycle 1, 3, and 5. The roadmap would then describe how to assess the abdominal girth per study preference, such as by having the patient lay flat on their back and the measurement to be taken following the line of their umbilicus. Performing these observations as described in the roadmap allows for consistent data and reflection, in relation to the investigational therapy. It is necessary to follow these three principles for optimal protocol adherence, which can provide best practice and possibly prove the best possible outcome in the study.

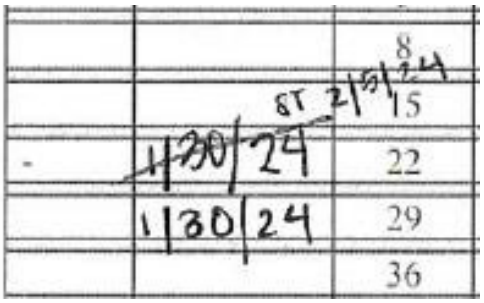
Side Effects and Adverse Events

Side effects and adverse events are very similar terms with a few distinct differences. Side effects are effects on the body that occur due to the administration of a medication, that are "unintended and the effects from the casual capacities or invariances of an intervention" (Due, 2023, p. 19). An adverse event, however, "is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medical treatment or procedure that may or may not be considered related to the medical treatment or procedure." (U.S. Department of Health and Human Services, 2017, p. 2). For example, a bedside nurse monitors and treats side effects as appropriate, such as fevers, nausea, anaphylaxis, or nerve pain. Then, it is the responsibility of the research nurse to interpret the documentation of these side effects, provided by the bedside nurse and the providers, to decipher appropriate adverse events that must be reported to the study per protocol guidelines because they are or are not related to the patient's treatment. Therefore, adverse events can be considered side effects but not all side effects can be considered adverse events. Not all side effects are deemed necessary to report either, but both documentation of side effects and reporting of adverse events are essential for effective patient care and research needs. Therefore, it is the bedside nurse's and provider's responsibility to document accurately and concisely in the medical records. Conversely, it is the research nurse's responsibility to report the data accurately to the study.

Understanding Documentation for Studies

Attributable, Legible, Contemporaneous, Original, Accurate (ALCOA) is an acronym and term that ensures data integrity within the research world (The University of North Carolina at Chapel Hill, n.d.). The best quality of records ensures the best outcomes for each study, and ideally the best outcomes for each patient. Patient documentation should include the elements of ALCOA, as it requires legibility, accuracy in reporting of all events, originality and attributability for who is treating and observing the patient. Good Clinical Practice (GCP) dictates how that documentation occurs (Vijayananthan & Nawawi, 2008). Most roadmaps are still designed to be used as a hard copy, and

therefore provide room for error through subsequent documentation. If any errors do occur on these roadmaps, errors can be corrected simply by three easy steps. First, the error is crossed out with a single line. Next, the person correcting the error takes ownership by placing their initials next to the crossed-out error. Lastly, the date the error was corrected is written in, beside the crossed-out error and initials. (See Figure 2). By following this standard of error correction, effective communication occurs between team members and study staff as to what was corrected, when, and by whom.



The date the dose was administered was written on the wrong date, and therefore the error was **crossed out with a single line**, the **initials**, and the **date it was corrected** are written in beside it. The corrected error was fixed by being written on its correct line, as seen below the error.

(Fig. 2, Good Clinical Practice Error correction. *Created by Shelly Tolley*.)

The Future of Pediatric Hematology/Oncology Nursing

Pediatric Hematology/Oncology Nursing has been shaped by survival rates and designated treatment courses. Chemotherapy regimens have grown from single to concomitant therapy, and some treatments have successfully combined multi-modal treatments such as radiotherapy, surgery, stem cell transplantation, and/or immunotherapy. The future of pediatric hematology/oncology nursing practice will continue to be shaped by research, which includes the world of immune-related therapies, such as biotherapies and targeted treatments, and of enhancing genetic codes. Updated treatments can include a drug combination of established chemotherapies into one drug (i.e., CPX-351, from the study AAML1421), or targeting specific molecular sequences by combining a host of commercially available medications (i.e., the MATCH screening trial and subsequent treatment trials). Genetic code can be changed through using a CRISPR technique (for example, Casgevy used to treat sickle cell disease by replacing the sickling gene present in sickle cell patients) (NIH, 2023; NIH, 2024; U.S. Food & Drug Administration, 2023). Through this technique, as the genetic code is altered, the body accepts this new code, and transmits it into red blood cell production, and therefore produces effective red blood cells that avert vaso-occlusive crises associated with sickling events (Park, 2023; U.S. Food & Drug Administration, 2023).

Conclusion

As caregivers, nurses, and advanced nursing practice providers, we all contribute to the future of Pediatric Hematology and Oncology patients. I hope that someday as pediatric hematology/oncology nurses, we can all view ourselves as contributors to research and are considered research nurses because of it. We maintain the best clinical practice, administer new treatments, and provide significant data, not only for our current patients, but our future patients as well. We are all truly research nurses and we all contribute to the science and outcome thereof.

Case Study

Now, take what was learned and apply that knowledge into the following case study.

Background: Dinutuximab is a monoclonal antibody used to treat high-risk neuroblastoma. In the last two decades, it has been proven as an effective treatment in some areas of this disease, and research continues to verify its effectiveness as a standard of care treatment. As a monoclonal antibody, it targets a specific antigen receptor known as GD2 (UpToDate, 2024). Nerve cells also express the GD2 receptor, and therefore nerve cells are inadvertently targeted as well (Herring et al., 2019). This can cause intense pain during administration of the medication. Reportable adverse events include urinary retention, elevated liver enzymes, increased endocrine dysfunction, psychiatric and neurological toxicities including reversible posterior leukoencephalopathy syndrome, and ophthalmic damage (UpToDate, 2024).

1) Your patient, Lyddie, is a 3-year-old who was just diagnosed with High-Risk Neuroblastoma and was enrolled on the study NB123.

Test yourself:

Question: Before ANY therapy can start, what needs to be done?

Answer: Any baseline specimens, genetic or molecular identification specimens, or other pre-treatment observations.

2) Lyddie, has completed Cycle 1 of treatment. She has now been randomized to the experimental arm of treatment, Arm B, in which she will receive topotecan, cyclophosphamide, and dinutuximab, followed by GM-CSF and G-CSF dosing. When double checking the chemotherapy, as the nurse, you notice the roadmap has some errors written on it.

Test yourself:

Question: What is the best clinical practice way to correct the errors?

Answer: Crossing out the errors with a single line and placing the initials of the individual making the correction next to the error, with the date of the correction written next to that. See example: ~~error on roadmap~~ ST 4/16/24 (or see Figure 2).

3) Once Lyddie starts receiving her dinutuximab dose, she becomes irritable and inconsolable. Mom is not sure why she is so fussy and tries to lay her down for a nap to help.

Test yourself:

Question: Why is this patient likely irritable and inconsolable?

Answer: She is likely experiencing nerve pain due to the medication.

Question: As your patient is complaining of pain, what is your priority as her caregiver?

Answer: To identify the source of the pain, treat your patient with support medications such as analgesics.

Question: For study purposes, what needs to be included in documentation about this side effect?

Answer: Documentation elements to include are signs and symptoms of pain, location of pain, what is used to treat the pain, as well as the patient's response to these supportive cares, and if there is any symptom recurrence or complete resolution.

4) Lyddie's pain has resolved, and she has moved forward in her treatment. After a couple weeks, Lyddie returns to the hospital to receive her next dose of dinutuximab. During her time at home away from the hospital, she has been doing well except for some days right after where she had abdominal pain, diarrhea, and vomiting. You notice her vital signs currently show a high heart rate for her age, and a fever. Lyddie is not as playful as she normally is.

Test yourself:

Question: What is your first priority with Lyddie?

Answer: Always treat the patient first for current symptoms, per institution standards and for patient safety. This can include admitting the patient, administering antibiotics, and obtaining blood culture and possibly stool specimen samples.

Question: From a study standpoint, what needs to be completed and documented?

Answer: Documentation should include complete vital signs (as well as highs and lows of vital signs), any indicated protocol lab specimens, signs, symptoms, and the timeframe of illnesses. If an infectious process specimen is obtained, look for the results and make sure those results are included in the

documentation. Make sure lab specimen and standard of care lab specimens have resulted and included in documentation.

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