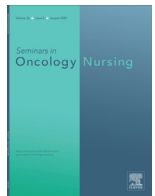




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Hypersensitivity and Chemotherapy Desensitization

Dallas Lawry, BSN, RN, OCN®, Allegra Bell, MSN, RN, OCN®, Amanda McKaig, BSN, RN, OCN®, Rayna McParlane, BSN, RN, OCN®

UCLA Santa Monica Medical Center, Santa Monica, CA

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ABSTRACT

Objectives: Hypersensitivity reactions (HSRs) are defined as reactions with reproducible signs and symptoms, triggered by an exposure to a stimulus at a dose tolerated by normal subjects. Although discontinuing the allergenic medication can eliminate the potential for HSRs, it can also lead to significant morbidity and mortality due to suboptimal treatment of the underlying disease. Therefore, desensitization protocols have been developed that offer a safe process that delivers full therapeutic doses in an incremental fashion without eliciting life-threatening reactions.

Data Sources: This article uses a case study to discuss the process of chemotherapy desensitization, associated complications, and identify areas of improvement in the management of HSRs within an academic medical center.

Conclusion: HSRs are a complex pathophysiologic response that requires an experienced oncology nurse at the bedside to manage potentially life-threatening symptoms.

Implications for Nursing Practice: Thorough education and training is needed among nursing staff to manage HSRs during the chemotherapy desensitization process.

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Chemotherapy Desensitization

In the ever-evolving world of cancer treatment, patients continue to be exposed to new chemotherapy drugs and monoclonal antibodies, both with the potential to induce a hypersensitivity reaction (HSR). HSRs are defined as reactions with reproducible signs and symptoms, triggered by an exposure to a stimulus at a dose tolerated by normal subjects.¹ The mechanisms beneath these responses can be immunologic or nonimmunologic. Most chemotherapy HSRs are type I, immediate reactions with immunoglobulin E (IgE)-mediated release of antibodies against the soluble antigen, resulting in cell degranulation, the release of histamine, and other inflammatory mediators.² Clinical presentations include cutaneous manifestations, flushing, pruritus, hypotension, sense of impending doom, nausea and vomiting, wheezing, dyspnea, and in severe cases, anaphylaxis.² Type II HSRs occur when immunoglobulin M (IgM) or immunoglobulin G (IgG) antibodies are directed against cellular or extracellular matrix antigens, resulting in cellular destruction, functional loss, or damage to tissue.¹ Clinical symptoms may present as hemolytic anemia, interstitial nephritis, or immune thrombocytopenia. Type III HSRs are caused by the accumulation of immune complexes and may take hours to several days to develop.¹ Type III hypersensitivity may present clinically as serum sickness or

Arthus reaction. Type IV hypersensitivity results in the contact of an antigen with presensitized T-lymphocytes, provoking an inflammatory reaction clinically presenting days after as contact dermatitis or graft-versus-host disease. Once a patient has experienced an HSR, re-exposure to the allergenic medication can lead to the sudden systemic release of inflammatory mediators from activated mast cells and basophils, inducing an HSR and potentially life-threatening symptoms.^{1,2} Although discontinuing the allergenic medication can eliminate the potential for HSRs, it can also lead to significant morbidity and mortality due to suboptimal treatment of the underlying disease. Therefore, desensitization protocols have been developed that offer a safe process that delivers full therapeutic doses in an incremental fashion without eliciting life-threatening reactions.³ This allows patients with cancer to receive the most effective first-line treatment despite their HSR history. See Table 1 for chemotherapies and associated HSRs. The case study of patient RC allows health care providers to look at the complexities of the desensitization process from the perspective of the nurse and how critical interventions will dictate the course of immediate care and overall treatment plan.

Pathophysiology and the Immune System

The human body is regularly exposed to environmental toxins and infectious microorganisms, but the miraculous layers of immunity within our bodies are constantly fighting and protecting us from disease.⁴⁻⁶ A human's immune system is characterized by two

* Address correspondence to: Allegra Bell, MSN, RN, OCN®, UCLA Santa Monica Medical Center, Solid Tumor Program, 1250 16th St, Santa Monica, CA 90404
E-mail address: abell@mednet.ucla.edu (A. Bell).

Table 1
Chemotherapy Agents and Associated Hypersensitivity Reactions

Drug and Chance of Reaction	Description of Reaction	Prevention	Skin Test	Future Options After Reaction
Bleomycin (1%)	Between 50% and 60% of patients receiving bleomycin have a self-limited mild febrile reaction without any other symptoms; hyperpyrexia with wheezing, mental confusion, anuria, and hypotension; hypersensitivity pneumonitis	Pretreatment with acetaminophen and diphenhydramine	A test dose (IV injection of ≤ 2 units of bleomycin followed by monitoring of vital signs every 15 minutes for a minimum of 1 h) followed by administration of the remainder of the dose	—
Carboplatin (1%–19.5%) Mostly after cycles 6–8	Urticaria or angioedema, bronchospasm, hypotension, rash, mostly after cycles 6–8	Skin test after sixth cycle is recommended and validated; monitor later cycles and if the patient is restarting therapy after an interval > 2 years	Intradermal injection of 0.02 mL of undiluted form of the carboplatin preparation planned for infusion	Desensitization
Cisplatin (1%–5%)	Mild to severe to lethal urticaria or angioedema, bronchospasm, hypotension, rash	Skin test is not recommended or validated	—	Possible desensitization; more experience is needed
Cytarabine	“Cytarabine syndrome”: flulike syndrome consists of fever, rigors, diaphoresis, myalgias, arthralgias, conjunctivitis, a macular skin eruption, and occasionally, hypotension; rarely anaphylaxis with angioedema, urticaria, hypotension are reported; hand-foot syndrome	A dose of acetaminophen prior to and following each day's drug infusion may reduce the frequency of the cytarabine syndrome; glucocorticoids may also be beneficial for both treatment and prevention	—	Desensitization; retreatment after cytarabine syndrome can be safely accomplished with increased premedication
Docetaxel (30% during first or second dose)	Dyspnea, hypotension, bronchospasm, urticaria, rashes, edema	Premedicate with dexamethasone 16 mg/d for 3 days, starting 1 day before chemotherapy	—	Substitution with paclitaxel if clinically appropriate
Doxorubicin Incidence only in liposomal daunorubicin and pegylated liposomal doxorubicin (9%–14%)	Flushing and chest pain, hypotension, and dyspnea, other combinations	Both the localized flare reaction and generalized infusion reaction can be successfully blocked by pretreatment with diphenhydramine and glucocorticoids; reconstitution of doxorubicin in saline rather than distilled water can decrease the frequency of local flare reactions	—	Desensitization
Epipodophyllotoxins Teniposide: (4%–6%, mostly grade 1 or 2) Etoposide (<2%)	Hypotension, dyspnea, bronchospasm	Slowly infuse for 30–60 min	—	Rechallenge after premedication with antihistamines and steroids
L-Asparaginase (5%–8% but increases to 33% after fourth dose)	Urticaria or angioedema, bronchospasm, hypotension; serious anaphylactic reactions occurring in less than 10% of patients	Skin test is not validated; some experts state the skin test is of no use because of the high rate of false-positives and false-negatives	Intradermal injection of 0.1 mL of a 20 IU/mL dilution of asparaginase	Desensitization or substitution with a different preparation (<i>Escherichia coli</i> , <i>Erwinia</i> , Polyethylene glycol)
Oxaliplatin (0.5%–25%) Reaction after several cycles	Urticaria or angioedema, bronchospasm, hypotension, rash, hemolytic anemia, cytokine release syndrome	Skin testing is reported to be 75%–80% accurate but not validated	European Academy of Allergy and Clinical Immunology recommends a skin test at 5 mg/mL for prick test and 0.05 mg/mL and 0.5 mg/mL for intradermal test.	Desensitization
Paclitaxel (2%–4%) Develops with first or second dose	Urticaria or angioedema, bronchospasm, hypotension	Premedications with antihistamines, steroids, and ranitidine	—	Desensitization with standard 12-step program if rechallenge caused a reaction; substitution with docetaxel if clinically appropriate.
Procarbazine (6%–18%)	Maculopapular rash, urticaria, cough, angioedema, interstitial pneumonitis	No reliable prevention exists	—	Discontinuation of drug

IV = intravenous.

Based on information from Castells, Matulonis, Horton, 2020; Jakel et al, 2016; Kroschinsky et al, 2017; Lax et al, 2015; Olsen et al, 2019 With permission from Pattie Jakel MSN, RN, AOCN®.

distinct systems: innate immunity and adaptive immunity. Innate immunity is defined by the inflammatory process and the protective physical barriers of the body.^{4–6} Innate immunity is nonspecific and is carried out virtually the same way regardless of trigger or insult.^{4–6} Adaptive immunity constitutes memory and the ability to resist diseases with subsequent encounters.^{4–6}

The pathophysiology of HSRs, including allergic reactions, begins with *sensitization* and the basic process of inflammation. To understand the cause of HSRs resulting in various types of anaphylaxis, it is crucial to consider a brief overview of immunology and the chemical players in an inflammatory allergic response. Both innate and adaptive immune systems participate in allergy-induced HSRs.^{4–6}

Overview of Innate Immunity

Innate immunity, also known as native or natural immunity, includes two lines of defense: natural barriers and inflammation.⁴⁻⁶ The first line of defense is natural barriers.⁴⁻⁶ Natural barriers line the entrances to the body with layers of epithelial cells or biochemical substances and include the skin, mucus membranes, and the acidity of the stomach.⁴⁻⁶ If a pathogen or injury breaks through these surface barriers, the second line of defense activates the inflammatory response.⁷⁻⁹ The inflammatory response includes inflammation, vascularization, protein cascade systems, and specialized cells.⁴⁻⁶

Inflammation

Cellular or tissue damage can be caused by a wide variety of sources such as “mechanical injury, infection, ischemia, nutrient deprivation, chemical agents, temperature extremes, or radiation.”⁴⁻⁶ Inflammation is therefore a nonspecific process, meaning it occurs essentially the same way regardless of stimulus or previous sensitization. Systemic manifestations of acute inflammation include fever, leukocytosis, and plasma protein synthesis.⁴⁻⁶

Vascularization

The cardinal signs of inflammation are redness, heat, swelling, and pain.⁴⁻⁶ This tetrad of symptoms characterizes the vascular nature of the inflammatory process. Particularly, inflammation includes *vasodilation*, *vascular permeability* (leakage of fluid), and *diapedesis* (white blood cell adherence and migration through vessel walls to sites of injury).^{4-6,10} After injury or insult occurs, increased blood flow to the area and capillary permeability cause a leakage of plasma, leading to edema.^{4-6,10} The resultant increased red blood cells at the site cause warmth and redness.⁴⁻⁶ Simultaneously, biochemical mediators such as histamine and bradykinin are being circulated, and white blood cells are adhering to vessel walls and entering the site, perpetuating the process.^{4-6,10}

Plasma Protein Systems

The complement system, clotting system, and kinin systems are the plasma protein systems essential to activating the inflammatory response.⁴⁻⁶ Many of the proteins within this system exist as no-active forms (proenzymes) that are only activated by another chemical within the cascade.⁴⁻⁶ The complement cascade has complement proteins, most notably C3a and C5a, which are considered anaphylatoxins that induce rapid mast cell degranulation.^{4-6,10} Mast cell degranulation releases granular contents and histamine, causing profound vasodilation and capillary permeability.^{4-6,10} C3a also releases a biochemical substance to attract leukocytes to the site.⁴⁻⁶ The primary product of the kinin system is bradykinin, which dilates blood vessels, works in concert with prostaglandins to simulate nerve endings that signal pain, and cause smooth muscle retraction, which leads to increased vascular permeability and leukocyte chemotaxis.⁴⁻⁶

Cell Mediators of Inflammation

The cells of the inflammatory response secrete and respond to biochemical mediators produced by the complement system, cellular injury, or microbes themselves.⁴⁻⁶ Leukocytes are further categorized into granulocytes (basophils, eosinophils, and neutrophils), monocytes (precursors to macrophages), and lymphocytes (NK cells, T cells, B cells).⁴⁻⁶ Macrophages and lymphocytes produce the cytokine interleukin-1 (IL-1); IL-1 is the cause of fever for infectious and inflammatory responses.⁴⁻⁶

A predominant white blood cell in inflammation is the mast cell.⁴⁻⁶ Mast cells *degranulate* and release potent chemicals (histamine) that induce inflammation and allergic responses.^{2,4-6,11,12} They are also responsible for the release of eosinophil chemotactic factor of anaphylaxis (ECF-A), which calls eosinophils into play during allergic anaphylaxis (the cause of eosinophilia that is seen in allergic

pathologies).⁴⁻⁶ All of these cells act separately and in combination for various immune reactions.⁴⁻⁶

Hypersensitivity (Allergy)

Drug hypersensitivity exists on a spectrum, from mild cutaneous reactions to potentially deadly systemic reactions such as anaphylaxis.¹⁰ Anaphylaxis incidence is about 0.4% to 3.1%, with a mortality rate of 0.65%.¹⁰ HSRs are categorized into four distinct types of immune mechanisms: Type I (IgE-mediated), Type II (tissue-specific HSRs, IgG-mediated), Type III (IgG immune-complex mediated HSRs), and Type IV (T cell-mediated HSRs).^{4-6,10} Often, more than one mechanism is at work during an allergic reaction.⁴⁻⁶

When the intricacies of the immune system go awry, the possible outcomes include allergic reactions and autoimmune disorders.⁴⁻⁶ Hypersensitivity is a disordered immune response that produces an exaggerated reaction to an antigen.⁴⁻⁶ Antigens are molecules that react with antibodies or antigen receptors on B and T cells; an antigen that induces an allergic reaction is commonly called an *allergy*.⁴⁻⁶ IgE is the antibody with specialization for allergic responses.^{4-6,12} The most severe form of a HSR is anaphylactic shock.^{4-6,13}

Sensitization, Priming, and Becoming Allergic

For the purposes of this article, the antigen is an *allergen*. Allergens are usually benign and might be a food, pollen, or a drug—in this case, a chemotherapeutic agent.⁴⁻⁶ To become “allergic” to something, a person must first be *sensitized* to the agent.⁴⁻⁶ Sensitization occurs after one or many exposures and can occur rapidly or over the course of several years.⁷⁻⁹ If an antigen causes adequate antibody or T cell response, re-exposure to said antigen results in a noticeable allergic reaction.^{4-6,12}

First, initial exposure to the allergen occurs.^{2,11} Next, antigen presenting cells present this allergen on the cell surface and carry it to lymphoid tissue (T cells) where sensitization begins.^{2,11} These T-helper cells inform and activate B cells to become plasma cells.^{4,7,8} With the help of interleukin-4 (IL-4), these primed plasma cells will now secrete IgE that is specific to the said allergen.^{2,10,11} The IgE molecule has a heavy chain and a light chain the light chain binds to mast cells (degranulate and release histamine), and the heavy chain binds to the surface of basophils (produce IL-4).^{2,10,11} Now that IgE with a specific affinity for an allergen exists in the body, the sensitization process to a particular allergen is complete.^{2,11,12}

The Pathophysiology of Hypersensitivity

Hypersensitivity is an umbrella term that covers any reaction that goes beyond that which is usually tolerated by normal subjects.¹⁴ These reactions might be allergic or nonallergic.¹⁴ However, in all of these reactions, regardless of trigger (immune or nonimmune), there is an unexpected and rapidly developing, sometimes lethal, systemic reaction.^{10,14} Anaphylaxis is a severe type of HSR that typically involves more than one organ system.⁴⁻⁶ In alignment with this literature, Kemp¹² describes anaphylaxis as an “acute, potentially lethal, multisystem syndrome that results from the sudden release of mast cell- and basophil-derived mediators into the circulation.”^{10,15,16} These chemical mediators include histamine, tryptase, chymase, heparin, and other cytokines (tumor necrosis factor [TNF] and IL-4).^{12,14}

There is a literary consensus that *allergic anaphylaxis* is an immediate, antibody-mediated (IgE), Type I HSR.^{2,10-12,14} It is an allergic response that occurs when primed IgE on mast cells begins an explosive and inappropriate immune reaction.^{2,11,14} In general, allergic HSRs are “antigen specific” because the immune system has already been primed and sensitized against this antigen.^{2,11} Thus, the next time this antigen (allergen) is introduced, the body now produces an exaggerated and inappropriate immune response, a reaction that is truly *hypersensitive*.^{2,11}

On subsequent exposure to the same or similar antigen, the bound IgE on mast cells recognizes the allergen, causing mast cell degranulation and histamine release within minutes.^{2,11,12,14} The histamine then causes vasodilation and increased vascular permeability, which is the reason for hypotension and flushing.^{2,11,14} The biphasic reaction (late reaction) of Type I HSRs causes the release of leukotrienes (increasing vascular permeability and bronchoconstriction), prostaglandins (causing bronchoconstriction), and eosinophil chemotactic factor of anaphylaxis (attracting eosinophils immediately).^{2,11,12,14} All of these chemical mediators cause the signs, symptoms, and eosinophilia for local and systemic allergic reactions.^{2,11,12} Type I HSRs can occur immediately within minutes to hours or be delayed over several hours to days.^{4-6,10} Anaphylaxis is the most rapid and severe Type I HSR; it is an explosive and systemic inflammatory response that occurs within minutes of re-exposure to an allergen and is life-threatening.^{4-6,10}

It is the process of HSR that is harmful and not necessarily the allergen.⁴⁻⁶ If all of these mechanisms activate the “chain reaction” of allergic inflammation, anaphylaxis can ensue.¹² Imagine the four cardinal symptoms of inflammation occurring within multiple organ systems simultaneously and synergistically; this is the basis of anaphylactic shock, and the rapid process by which an allergy can be fatal. If an allergen triggers *widespread hypersensitivity*, the inflammatory and vasodilatory effects are massive and pathologic. Extreme vasodilation, peripheral pooling, and hypovolemia lead to decreased tissue perfusion and finally impaired cellular metabolism—the origins of shock.^{4-6,13}

Treatment/Nurse Management

Since 2012 the University of California, Los Angeles (UCLA) has conducted chemotherapy desensitization.² This medical procedure follows a strict hospital-wide protocol that is based on research and scientific literature. The desensitization process is personalized to each patient through the collaboration between the allergy and oncology medical teams.

Preadmission

Patients that qualify for chemotherapy desensitization are those who have previously experienced severe hypersensitivity reactions to their treatment. It is determined by the primary oncologist that this medication provides potential life-saving or life-prolonging benefits that thus overrules the risk of allergic reaction. The desensitization process is based on highly structured protocols that ensure the safety and well-being of the patient. Nonetheless these protocols are highly labor-intensive and require an experienced oncology nurse within an acute care setting.

The desensitization process requires consultations from the allergy specialty and a scheduled admission date to accommodate these unique requirements.

Admission

Patients are admitted 24 hours in advance of their infusion to receive their premedications and to ensure all measures are in place for the desensitization procedure.² The patient is admitted to an acute care oncology unit or the intensive care unit; this is determined by the severity of their previous reaction and medical needs.² The patient will have a 1:1 nurse-to-patient ratio with an experienced oncology nurse who is certified in chemotherapy and biotherapy administration; it is highly preferred that the assigned nurse also has an oncology nurse certification.² The 1:1 ratio is maintained during the duration of the drug administration and the 2-hour postinfusion monitoring period. It is the nurse's responsibility to inform the multiple interdisciplinary teams that the patient has arrived; this includes the oncology team, allergist, pharmacy, and respiratory therapist. The respiratory therapist will assess the patient's baseline respiratory

status and obtain a peak expiratory flow volume. Both medical teams will consult with the patient upon admission to discuss the plan of care and complete a full physical assessment.²

It is pertinent that the primary nurse of this patient prepares the room in advance for the desensitization the following day. Preparation includes ensuring that all emergency equipment be readily available at bedside, including a face mask, nasal cannula, cardiac monitor, nebulizer, and suction canister.^{2,8} The admitting nurse verifies that the emergency medications and premedications have been ordered to ensure patient safety. This verification process can save time for the medical team and create a more seamless process with less delays in care for the person affected by cancer. The premedication process is started the night prior to the administration of the chemotherapy and is personalized to the patient's specific needs. The same premedications will be administered the next morning 30 minutes prior to the start of treatment.² A sample list of these premedications and emergency medications can be found on the desensitization checklist.² The morning of the desensitization the patient is placed on both cardiac and oxygen monitoring.^{3,4}

Administration

The chemotherapy treatment is divided into three or four separate solutions (A, B, C, and D). The initial bag is approximately 1000 times less concentrated than the standard chemotherapy preparation; each bag becomes more concentrated than the last.¹⁷ All chemotherapy is delivered by pharmacy at a scheduled time that has been determined by the pharmacist and primary nurse. The chemotherapy will be delivered in clearly labeled bags with a primary line primed with drug that is being desensitized; this is critical because the process is timed and drug should be delivered immediately. The protocol consists of a 12- to 16-step titration process with each titration time ranging between 15 and 20 minutes with the exception of the last step.¹⁷ The only bag to be fully infused is the last solution containing the 1:1 concentration. Each step infused will total the standard dose. Total infusion time can last between 5.6 and 8.4 hours; however, if a reaction occurs, this could significantly prolong the desensitization process.²

Assessment

The desensitization protocol requires a detailed assessment prior to each up-titration of the medication being infused. It is important that prior to starting the infusion, the nurse will complete a full assessment with vital signs to gather a baseline for their patient.² With each up-titration the nurse will complete a set of vital signs and a pulmonary function volume measurement. The pulmonary function volume must be within 15% variance of the baseline volume to titrate to the next step.² It is crucial that the nurse remains at the bedside during the entirety of the procedure and be hypervigilant of the patient for possible signs of HSR. Subtle symptoms might first appear as mild or even insignificant to the untrained and inexperienced eye, making the need for a highly experienced nurse a necessary component for a safe desensitization.

The most common symptoms that occur at the start of HSR include but are not limited to mild cough, anxiety, restlessness, change in throat sensation, acute headache, tinnitus, acute nausea, or emesis.^{11,15} In addition, cutaneous manifestations are also frequently reported at the start of HSRs; these include sudden onset of generalized urticaria, angioedema, flushing, and pruritus.¹⁵ In the case of a reaction, the primary nurse must immediately stop the infusion, administer emergency medication, notify the allergist team, and provide supplemental oxygen or nebulizer treatments as needed.^{2,6} Emergency medication must be given based on the specific type of reaction and must be swiftly administered to stop the reaction from progressing. During an HSR, the most common combination of emergency medication includes intravenous H1 antihistamine (diphenhydramine or cetirizine), H2 antihistamine (famotidine), and a glucocorticoid (methylprednisolone).^{8,15} If the reaction continues to progress into anaphylaxis, the patient may present with stridor,

wheezing, dyspnea, increased work of breathing, persistent cough, cyanosis, persistent vomiting, abdominal pain, hypotension, dysrhythmia, chest pain, and collapse.^{2,15,17} Intramuscular epinephrine is the gold standard in treating anaphylaxis, and it is important to remember that there are no contraindications to epinephrine in the setting of anaphylaxis.^{2,15,17} Once the reaction has subsided, the patient can resume the infusion. However, the allergist must give the primary nurse permission to resume treatment and may ask to restart the infusion at the previously tolerated step. When the infusion is complete, the patient will continue to be closely monitored and assessed every 30 minutes for an additional 2 hours.^{2,4} During the postinfusion observation period, no other chemotherapy agents can be given. Table 2 presents the National Cancer Institute (NCI) grading of adverse events.

Once patients have completed the desensitization procedure and is medically cleared by both the allergy and oncology team, they can be safely discharged home. It is crucial that the oncology nurse educates patients at this time about the signs and symptoms of a delayed reaction and instruct them to call 911 immediately if they experience such symptoms.²

Training Staff to Desensitization

Multiple root cause analyses were conducted on desensitization patients due to poor patient outcomes. Keeping up to date with best practices, it was decided by the solid oncology unit at the UCLA medical center in September 2018 that the desensitization training process would become more in-depth than the previous training model. The staff of the oncology unit also expressed the need for restructuring of and re-educating on the desensitization process.

To accommodate these new requests a nurse experienced in desensitization was paired with a trainee during their first desensitization process (a model still continuing in practice). It is the responsibility of the experienced nurse to educate the trainee by introducing the correct resources needed to monitor the patient safely and effectively. In addition, the experienced nurse explains the need for constant communication with pharmacy and the allergy team. A desensitization checklist was also created as a clinical reference tool to use during this procedure. This checklist is a concise document created by the nursing staff in collaboration with the UCLA allergist team. It is written in a step-by-step format to help guide the nurses on the proper practice of desensitization and is used as a tip sheet for which emergency medications are best suited for a variety of reaction symptoms. This checklist must remain at bedside during the patient's hospitalization. This new structure has provided the oncology team with a more in-depth and supportive training process. The result has been a group of nurses that are more confident in the care of these high-acuity patients.

Case Study

Introduction/Background

RC is a 35-year-old female with a past medical history of inflammatory bowel disease (IBD), metastatic colon adenocarcinoma, and environmental allergies. She had previously undergone a colectomy with diverting ileostomy, followed by six cycles of adjuvant leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin (FOLFOX) chemotherapy regimen. She has a history of multiple oxaliplatin reactions with her most recent reaction causing chest pain, dyspnea, hypoxia, and hypotension (Type 1 HSR), at which point FOLFOX was discontinued. She then completed seven cycles of leucovorin calcium (folinic acid), fluorouracil, and irinotecan hydrochloride (FOLFIRI)-cetuximab, and regorafenib/nivolumab, with a subsequent computed tomography (CT) showing disease progression in the liver. At this time, RC presents to the inpatient unit for FOLFOX and Bevacizumab, where she will undergo a rapid drug desensitization (RDD) for oxaliplatin.

What Are RC's Risk Factors for a Reaction?

*History of atopy, history of chronic inflammation from IBD, receiving a platinum agent, history of prior reaction, multiple cycles of the same medication, and intravenous administration.*¹⁸

Case Presentation

Informed consent was obtained from the patient.

The night before her desensitization, RC received the following by mouth:

- 40 mg prednisone
- 10 mg cetirizine
- 40 mg famotidine
- 10 mg montelukast

The following morning of her desensitization, RC received by mouth

- 40 mg prednisone
- 10 mg cetirizine
- 40 mg famotidine
- 10 mg montelukast
- 650 mg acetaminophen

and received intravenously

- 25 mg diphenhydramine

Table 2

Common Terminology Criteria for Adverse Events Grading for Allergic Reaction, Anaphylaxis, and Cytokine Release Syndrome

Adverse Event	Grade				
	1	2	3	4	5
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; IV intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Anaphylaxis	—	—	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% O ₂	Hypotension managed with one pressor; hypoxia requiring ≥40% O ₂	Life-threatening consequences; urgent intervention indicated	Death

IV = intravenous; O₂ = oxygen.

From *Common Terminology Criteria for Adverse Events* [v.5.0], by National Cancer Institute Cancer Therapy Evaluation Program, 2017. Retrieved from <https://www.upToDate.com/contents/infusion-reactions-to-systemic-chemotherapy#H20>.

Name of Medication	Oxaliplatin					
Target Dose	173.4 mg					
Standard Vol per bag	250 ml in D5W					
Final rate of infusion	70 ml/hr					
			Concentration	Solution	Amount (in mg) to be mixed in 250ml D5W	
			1/100th target	A	1.7	0.006936
			1/10th target	B	17	0.06936
			target	C	173	0.6936
Solution	Step	Rate (ml/h)	Time (min)	Solution	Administered Dose (mg)	Cumulative Dose (mg)
A	1	2	20	A	0.00	0.00
A	2	5	20	A	0.01	0.02
A	3	10	20	A	0.02	0.04
A	4	20	20	A	0.05	0.09
B	5	5	20	B	0.12	0.20
B	6	10	20	B	0.23	0.43
B	7	20	20	B	0.46	0.89
B	8	40	20	B	0.92	1.82
C	9	10	20	C	2.31	4.13
C	10	20	20	C	4.62	8.76
C	11	40	20	C	9.25	18.00
C	12	70	193	C	156.18	174.18
		totals	413	min	174	
		estimated time	6.9	h		

Note last bag will be infused until completion unless heme onc attending says otherwise--time provided is estimate

19:20 RC became febrile with a temperature of 37.9°C. (100.22°F). She was tachycardic to 130 s. There was no change in blood pressure (BP) or respiratory status at this time. The night coverage physician was notified of the fever.

Opportunity for Improvement: The allergist should also have been notified at this time

19:40 RC complained of feeling anxious; lorazepam 1 mg by mouth was given. The patient had her first episode of hypoxia with an oxygen saturation level of 88%. She was placed on 2 L supplemental oxygen.

Opportunity for Improvement: Anxiety or an impending sense of doom, as well as hypoxia, can be clinical indicators of anaphylaxis.¹⁵ Giving lorazepam and placing the patient on supplemental oxygen can help treat RC's symptoms but do not treat the underlying cause. The allergist should have been notified; epinephrine, epinephrine racemic, and albuterol could have been given.

20:10 RC's heart rate increased to 140 s. The night coverage physician is notified again. Due to the fever, tachycardia, and decreased oxygen saturation, an infectious workup is completed.

Blood cultures and a lactate were drawn, a urine culture was obtained, and the patient was started on intravenous antibiotics (cefepime).

Opportunity for Improvement: RC is showing signs of anaphylactic shock; however, many conditions have systemic effects that mimic anaphylaxis.¹⁸ Different types of shock have similar presentations. The concern seems to be for septic shock, but neither the nurse nor the physician contacted the allergist to also consider anaphylactic shock.

21:00 Marked the end of the observation period.

24:00 RC remained febrile overnight with a maximum temperature of 39.8°C (103.64°F). Additional acetaminophen was given.

04:30 First episode of hypotension occurs with a BP 79/48. The night covering physician was notified. The patient received IV fluid resuscitation between 05:00 and 08:00 (total of 3 L lactated Ringer solution), with initial improvement of her BP to 100 s/60 s, but then subsequent dropped to 80 s/50 s. The morning labs that were drawn showed abnormalities in a lactate of 33 mg/dL, a creatinine of

1.67 mg/dL (baseline of 0.6 mg/dL the day before), and a carbon dioxide of 17 mmol/L.

Opportunity for Improvement: The patient is showing signs of anaphylactic shock. Hypotension, hypoxia, and elevated creatinine demonstrate multiorgan dysfunction. Epinephrine and antihistamines should have been given by this point. The allergist should have been notified.

During this time, change of shift occurred again with the primary team arriving in the morning.

Management/Outcomes

08:00 RC's BP remained in 80 s/50 s, tachycardia into 120 s to 130 s, with neck and facial flushing noted. The allergist and primary oncology nurse practitioner were immediately notified of the overnight events. Intramuscular epinephrine 0.3 mg, and intravenous diphenhydramine 25 mg, famotidine 20 mg, and methylprednisolone 62.5 mg were given. RC was noted to only have 75 mL of urine output overnight, despite receiving 3 L of intravenous fluid.

09:15 Allergist at the bedside to assess the patient. BP improved to 90 s/60 s. An additional two doses of intramuscular epinephrine 0.3 mg were given based on RC's weight. Oral diphenhydramine 25 mg, cetirizine 20 mg, and famotidine 20 mg were also given, with an additional 1 L bolus of lactated Ringer solution. A tryptase, C-reactive protein (CRP), and procalcitonin were drawn and sent to the lab, with results showing tryptase 7 ug/L, C-reactive protein 10.3 mg/dL, and procalcitonin: 18.07 ug/L.

Over the course of the next hour, RC's systolic BP improved into the 90s to 100s. There was concern for acute renal failure due to the increased creatinine with minimal urine output. The patient was transferred to the intensive care unit for further management.

Discussion

What Type of HSR Did RC Demonstrate?

RC truly demonstrated a "mixed reaction," which consists of a Type I HSR (mast cell and basophil driven), as well as a cytokine release syndrome (T-cell driven).¹⁹ The Type 1 HSR was consistent with a biphasic anaphylaxis reaction, which is characterized by an initial reaction followed by subsequent reaction without further exposure to the allergen. This can occur anywhere from 1-78 hours after the initial reaction.⁷ In this case, RC's symptoms that could be attributed to the Type 1 HSR were flushing, shortness of breath, nausea, throat itching, hoarseness, and hypotension. The symptoms that can be attributed to cytokine release are fever, chills/rigors, and nausea.

Where Did the Break Down in Communication Occur?

There were multiple missed opportunities for the allergist to be notified. The initial breakdown occurred at the first febrile episode, then at the onset of hypoxia, and again when the patient became hypotensive. There were opportunities for both the nurse and the on-call physician to contact the allergist, including clear instruction with contact information in the desensitization protocol in the patient's chart.

What Could Have Been Done Differently?

The allergist should have been notified with any change in patient condition. The emergency medications could have been given earlier (albuterol, epinephrine, diphenhydramine, famotidine, methylprednisolone). Inadequate amounts or delayed administration of epinephrine are associated with biphasic events.⁷

Implications for Oncology Nursing

HSRs can be serious and life-threatening; however, so can cancer. Rapid drug desensitizations have allowed patients to receive potentially life-saving cancer treatment despite having an allergy to the medication. Desensitizations require extensive planning and training for all members of the interdisciplinary team, both prior to and during the procedure. It is important to note that HSRs can be subtle and sometimes difficult to distinguish from other side effects or disease processes. Not all serious reactions can be prevented, but early intervention can save lives.

A root-cause analysis was performed on this case to determine where the clinical errors occurred. As a result, further education was provided to clinical staff on the management of HSRs, and the desensitization training process for nurses was restructured. Failure to recognize and manage these serious reactions can lead to patients being unable to receive potentially curative treatment. Unfortunately, it was deemed unsafe for RC to receive further doses of this medication, and she was not rechallenged. She succumbed to her disease in December 2020.

This article was created in her memory.

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Rita Kachru, MD, Assistant Professor and Section Chief, Clinical Immunology and Allergy, David Geffen School of Medicine, UCLA.

Patricia Jakel, MSN, RN, AOCN®, Oncology Nurse Specialist, UCLA Santa Monica Medical Center, Solid Tumor Program.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.soncn.2021.151132](https://doi.org/10.1016/j.soncn.2021.151132).

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