ALERT
Don appropriate personal protective equipment (PPE) based on the patient’s signs and symptoms and indications for isolation precautions.

Refer to Oncology Nursing Society (ONS) interim guidelines for PPE recommendations during an emergent shortage of PPE (e.g., pandemic).

Acute hypersensitivity reactions may lead to death.

Only qualified physicians, physician assistants, advanced practice registered nurses (APRNs), or nurses with demonstrated competency administer antineoplastic therapies. Refer to the professional’s regulatory scope of practice and the organization’s practice.

OVERVIEW
Hypersensitivity reactions are unexpected and excessive responses of the immune system to a foreign substance (antigen) that cause a cascade of symptoms. Almost all chemotherapeutic agents can cause an allergic reaction. In recent decades, the frequency of hypersensitivity reactions has increased, especially in patients with cancer.

Four basic types of hypersensitivity responses may occur (Table 1).

<table>
<thead>
<tr>
<th>Hypersensitivity reaction</th>
<th>Definition</th>
<th>Example(s)</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>• IgE mediated (immediate)</td>
<td>• Anaphylaxis</td>
<td>• Minutes to generally within 1 hour after drug exposure</td>
</tr>
<tr>
<td>Type II</td>
<td>• Antibody mediated cytotoxicity (IgG, IgM, complement)</td>
<td>• Drug-induced hemolytic anemia</td>
<td>• Variable</td>
</tr>
<tr>
<td>Type III</td>
<td>• Immune complex mediated</td>
<td>• Systemic lupus erythematosus • Rheumatoid arthritis</td>
<td>• 1 to 3 weeks after drug exposure</td>
</tr>
<tr>
<td>Type IV</td>
<td>• Delayed or cell mediated</td>
<td>• Poison ivy rash</td>
<td>• 2 to 7 days after drug exposure</td>
</tr>
</tbody>
</table>

IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M

The most serious reaction to an antineoplastic medication is a type I reaction, also known as a true allergic (i.e., anaphylactic) reaction. A type I reaction usually includes urticaria, bronchospasm, rash, and hypotension. The severity of the reaction, which may vary according to the medication (Box 1), the route, and the rate of administration, can range from mild flushing to anaphylaxis to death.
Box 1 Antineoplastic Drugs Most Commonly Associated with Hypersensitivity Reactions

- Asparaginase
- Bleomycin
- Blinatumomab
- Carboplatin
- Cetuximab
- Cisplatin
- Docetaxel
- Doxorubicin
- Etoposide
- Interferons
- Interleukins
- Oxaliplatin
- Paclitaxel
- Procarbazine
- Rituximab
- Teniposide
- Trastuzumab


The symptoms, the incidence, and the speed of the reaction vary among medications and among patients. Usually, the faster the reaction occurs, the more severe it is. Certain characteristics increase the risk of a hypersensitivity reaction; therefore, all risk factors must be documented (Box 2).  

Box 2 Risk Factors for a Hypersensitivity Reaction

- Age (older age)
- Failure to take prescribed premedication for prophylaxis
- Female sex
- First infusion of monoclonal antibody
- Geographic location (higher rates of reaction to cetuximab in southeastern states)
- High lymphocyte counts
- Higher than normal chemotherapy or biotherapy doses
- History of allergies (e.g., foods, medications, bee stings)
- History of asthma
- History of autoimmune disease
- History of pulmonary infiltrates, cardiac, or pulmonary dysfunction
- IV route of administration
- Multiple cycles of drugs (e.g., carboplatin, cisplatin)
- Primary tumor type, such as chronic lymphocytic leukemia and mantel cell lymphoma
- Current medications (e.g., angiotensin-converting enzyme [ACE] inhibitors, beta blockers, opioids)

(Data from Dykewicz, M.S., Lam, J.K. [2020]. Drug hypersensitivity reactions. Medical Clinics of North America, 104[1], 109-128; Warrington, R., Silviu-Dan, F., Wong, T. [2018]. Drug allergy. Allergy, Asthma & Clinical Immunology, 14[Suppl. 2], 60.)
Hypersensitivity reactions are further classified as immediate (occurring within 1 hour of administration) or nonimmediate (occurring more than 1 hour after administration). Drug desensitization is currently used to define a process by which a patient’s immune response to a medication is modified to generate temporary tolerance. This process takes advantage of well-characterized inhibitory pathways in the body. The major risk during desensitization is anaphylaxis. Desensitization is generally favored for patients with severe reactions. Rechallenging a patient may be attempted in those who have had a mild hypersensitivity reaction.

With newer monoclonal antibodies and the development of chimeric antibodies, an increasing number of agents are being administered that can cause an acute infusion reaction. Acute infusion reactions are likely to remain as an ongoing potential adverse reaction from cancer treatment in the years to come. The risk of developing reactions to monoclonal antibodies depends on the humanization of the antibody. Fully human monoclonal antibodies have less risk of inducing a hypersensitivity reaction compared to chimeric antibodies with a variable amount of mouse origin sequences. Chimeric antigen receptor (CAR) T cells are currently approved for some B-cell malignancies and in clinical trials for other hematologic and solid tumor malignancies. One major adverse reaction limiting their use as a treatment is cytokine release syndrome (CRS). CRS is an uncontrolled systemic inflammatory reaction that can become life threatening. It is commonly observed following administration of immune-based biotherapy and not considered an anaphylactic reaction. CRS usually occurs with the first infusion within the first couple of minutes to days after infusion; most cases are successfully rechallenged by administering the medication again using a rechallenge protocol that slowly reintroduces the medication to the patient. T-cell engaging immunotherapeutic strategies, such as checkpoint blockade, bispecific antibodies, and CAR T-cell therapy, are associated with a high risk of CRS. Symptoms of CRS include headache; nausea, vomiting, or both; myalgia; fever; chills; and rigors; as well as symptoms similar to anaphylactic reactions (type I hypersensitivity reactions). Symptoms of an anaphylactic reaction are usually much more severe and develop in the first few minutes of an infusion. Targeted agents have been reported to induce life-threatening severe cutaneous reactions. These reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis, drug rash with eosinophilia, and acute generalized exanthematous pustulosis.

Type II hypersensitivity reactions, such as hemolytic anemia, or type III reactions, such as pulmonary toxicity, allergic alveolitis, or toxic epidermal necrolysis, may occur with chemotherapy or biotherapy. Delayed (biphasic) reactions, also known as type IV hypersensitivity reactions, may display symptoms several hours or days after an infusion. Educating patients and caregivers of potential symptoms to immediately report to the practitioner is important.

A test dose may be administered to drug-naive patients before the first dose of an antineoplastic agent to check for a potential allergic reaction in patients with significant risk factors for hypersensitivity or in patients who will receive a medication known to cause hypersensitivity reactions. Premedications such as acetaminophen, antihistamines, corticosteroids, and H2 blockers may also decrease the risk of and prevent a hypersensitivity reaction. Montelukast can be used in patients with prominent respiratory symptoms.
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Staying alert to signs and symptoms of a hypersensitivity reaction (Box 3), making accurate assessments, and providing prompt interventions are necessary to avoid a fatal outcome.

Box 3 Signs and Symptoms of a Hypersensitivity Reaction

- Abdominal cramps
- Angioedema
- Back pain
- Bronchospasm
- Chest pain
- Dizziness
- Dyspnea
- Erythema
- Feeling of impending doom
- Fever
- Flushing
- Hemolysis
- Hypertension
- Hypotension
- Itching
- Joint pain
- Laryngeal spasms
- Nausea
- Rash
- Shortness of breath
- Swelling of throat or tongue
- Tachycardia
- Thrombocytopenia
- Tightness in chest
- Urticaria


The severity of a hypersensitivity reaction must be graded correctly using the National Cancer Institute’s Common Terminology Criteria for Adverse Events. This grade assists the practitioner in deciding whether to discontinue the medication or to rechallenge the patient with it. Rechallenging may be successful, but it may also require a longer infusion time and more aggressive premedication. Emphasis should be placed on education efforts before the administration of cancer treatment and being prepared in the event of an acute infusion reaction.

EDUCATION

- Provide developmentally and culturally appropriate education based on the desire for knowledge, readiness to learn, and overall neurologic and psychosocial state.
- Inform the patient and caregiver about the antineoplastic treatment plan, dosing schedule, and potential toxicities.
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- Teach the patient the signs and symptoms of a hypersensitivity reaction (Box 3) and instruct him or her on when to seek additional care.
- Tell the patient and caregiver whom to notify if symptoms develop during or after an infusion.
- Provide the patient and caregiver with the practitioner’s contact information after business hours.
- Instruct the patient and caregiver to notify the practitioner if signs or symptoms of a delayed (biphasic) reaction develop.
- Encourage questions and answer them as they arise.

ASSESSMENT AND PREPARATION

Assessment
1. Perform hand hygiene and don PPE as indicated for needed isolation precautions.
2. Introduce yourself to the patient.
3. Verify the correct patient using two identifiers.
4. Assess the patient’s risk factors for a hypersensitivity reaction, including a history of allergies.
5. Assess the patient’s treatment plan for antineoplastic medications known to cause hypersensitivity reactions.
6. If premedication is recommended for a planned treatment regimen, determine whether it has been prescribed.
7. Obtain the patient’s baseline vital signs.

Preparation
1. Ensure that informed consent is obtained and available for review per the organization’s practice.
2. Ensure that the patient has patent IV access.

Rationale: A patent IV line allows a route for emergency medication administration and aggressive fluid resuscitation.

PROCEDURE
1. Perform hand hygiene and don gloves and appropriate PPE based on the patient’s signs and symptoms and indications for isolation precautions. Use the ONS interim guidelines for PPE recommendations during an emergent shortage of PPE (e.g., pandemic) (Table 2).

<table>
<thead>
<tr>
<th>Table 2 Oncology Nursing Society (ONS) Recommendations and Interim Guidelines for Personal Protective Equipment (PPE) Use During Pandemic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PPE</strong></td>
</tr>
</tbody>
</table>
| Gown | Disposable poly-coated gown | • Regular disposable gown (water resistant)  
• Cloth gown (facility laundered) for infection control and nonhazardous drugs |
| Mask | Mask with face and eye protection required only if splashing likely and for spill cleanup | • N95 mask for symptomatic or patients with COVID-19 and hazardous drug spills and cleanup  
• PAPR |
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<table>
<thead>
<tr>
<th>Eye protection</th>
<th>Mask with eye protection or goggles if splashing likely or spill cleanup</th>
<th>• Full facepiece air-purifying respirator or PAPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gloves</td>
<td>Double chemotherapy-tested gloves</td>
<td>• Single chemotherapy-tested gloves</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Double standard examination gloves</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single standard examination gloves</td>
</tr>
<tr>
<td>Shoe covers</td>
<td>Only in area for compounding hazardous drugs</td>
<td>• Work-only, washable shoes</td>
</tr>
</tbody>
</table>

COVID, coronavirus, PAPR, powered air purifying respirator; PPE, personal protective equipment
*Highest-level recommended practice based on supplies of available PPE

2. When no PPE shortage exists, don two pairs of chemotherapy-tested gloves; a long-sleeved, nonpermeable chemotherapy-resistant gown; and eye protection or a face shield if the possibility of contact with emesis or other bodily fluids exists.
3. Two practitioners or personnel approved to prepare or administer antineoplastic therapies verify the patient using two identifiers, confirm with the patient the planned treatment, and verify the medication name, dose, volume, rate and route of administration, expiration dates and times, and appearance and integrity of the medications.
4. Explain the procedure to the patient and ensure that he or she agrees to treatment.
5. Administer a test dose, if prescribed.
   a. Monitor the patient for adverse reactions.
   b. Ensure that safety equipment is nearby before administration of the dose.
6. Administer premedication, as prescribed, or ensure that the patient took prescribed oral premedications, or both.3

    Rationale: Premedications, such as corticosteroids, antihistamines, acetaminophen, and H₂ blockers, are used to decrease the risk of a hypersensitivity reaction.2

7. Remind the patient to immediately report signs or symptoms of a hypersensitivity reaction, including mild skin reactions, urticaria, mild shortness of breath, dizziness, chest pain, or simply not feeling “right.”
8. Administer the antineoplastic medication as prescribed.
9. Observe the patient for a hypersensitivity reaction throughout the infusion.
10. If signs of a hypersensitivity reaction occur, immediately stop the medication infusion.
    a. Ensure that one nurse stays with the patient while another health care team member notifies the practitioner or other emergency personnel.
    b. Assess and maintain the patient’s airway, breathing, and circulation. If cardiac arrest occurs, initiate cardiopulmonary resuscitation and call a code.
    c. Monitor the patient’s vital signs and oxygen saturation.
    d. Administer IV fluids as prescribed or per the organization’s practice. Observe a patient with comorbid conditions for fluid overload.
    e. Administer oxygen as prescribed or per the organization’s practice.13
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f. If the patient is experiencing hypotension, place him or her in the supine position and raise his or her legs.

   Rationale: Raising the patient’s legs shifts intravascular volume to the upper part of the thorax.13

g. For moderate to severe reactions, administer epinephrine as prescribed or per the organization’s practice. The recommendation is 0.3 to 0.5 mg intramuscularly at a 1:1000 dilution.13

h. For severe hypotension, administer additional vasoactive medications as prescribed or per the organization’s practice.1

i. Administer other medications as prescribed or per the organization’s practice.

   i. High-dose corticosteroids: Corticosteroids may be prescribed to decrease the duration of acute reactions and prevention of delayed reactions.10 Steroids are generally the initial treatment for CRS.

   ii. Antihistamines: Diphenhydramine4

   iii. Beta adrenergics: Inhaled albuterol or inhaled ipratropium is used for patients using beta blockers for bronchospasm.

   Rationale: Patients using beta blockers have a higher incidence of anaphylactic reactions and more severe anaphylactic reactions, as well as paradoxical responses to epinephrine.1

   iv. Histamine blocking agents13

   Do not use ranitidine due to its associated risk of cancer.15

11. Rechallenge the patient with the antineoplastic agent, as ordered.

   a. Consider the severity of the reaction before the rechallenge.
   b. Consider drug desensitization protocols.2
   c. Administer additional premedication as prescribed.
   d. Resume the infusion at a slower rate.2
   e. Slowly titrate the infusion rate.

12. Manage cutaneous manifestations with topical lidocaine, ice, or topical corticosteroids.13

13. Before discharge, educate the patient and caregiver about the signs and symptoms of a biphasic reaction, and instruct the patient to report any signs or symptoms and to call 911 and go to the nearest emergency department immediately.

14. Discard supplies, remove PPE, and perform hand hygiene.

15. Document the procedure in the patient’s record.

MONITORING AND CARE

1. After the patient is stabilized, monitor vital signs and oxygen saturation per the organization’s practice.

2. After stabilizing a patient with anaphylaxis, continue to observe him or her for a biphasic reaction.

3. After stabilizing a patient with CRS, observe him or her for at least 30 minutes.8
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4. Ensure that the patient and caregiver understand which signs and symptoms to report and which require an immediate emergency response.

5. Ensure that the patient and caregiver understand whom to contact if signs or symptoms of a reaction develop.

6. Ensure that the patient has a caregiver at home to help monitor for reactions.

7. Assess, treat, and reassess pain.

EXPECTED OUTCOMES
- Early recognition and prompt intervention
- Resolved hypersensitivity reaction
- Successful rechallenge with medication
- Successful completion of antineoplastic therapy

UNEXPECTED OUTCOMES
- Delayed recognition
- Unsuccessful intervention
- Death

DOCUMENTATION
- Premedications given
- Description of the reaction
- Interventions provided for the reaction
- Efficacy of the interventions
- Hypersensitivity reaction grade
- Education
- Patient discharge instructions
- Unexpected outcomes and related interventions
- Time interventions initiated and ended
- Patient’s response to the medication, including any adverse reactions

SPECIAL CONSIDERATIONS
- Patients who are unreliable historians (e.g., patients with memory deficits) may not recall previous allergic reactions; care history and assessment of these patients is critical.
- Patients on beta blockers may have a higher risk of anaphylaxis and more severe anaphylactic reactions.
- Patients on beta blockers may have a paradoxical response to epinephrine and may respond better to ipratropium or glucagon.

REFERENCES

ADDITIONAL READINGS

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Elsevier Skills Levels of Evidence
- Level I - Systematic review of all relevant randomized controlled trials
- Level II - At least one well-designed randomized controlled trial
- Level III - Well-designed controlled trials without randomization
- Level IV - Well-designed case-controlled or cohort studies
- Level V - Descriptive or qualitative studies
- Level VI - Single descriptive or qualitative study
- Level VII - Authority opinion or expert committee reports

Supplies
- Alcohol wipes
- Bag-mask device
- Automated external defibrillator or defibrillator
- Emergency medications
- IV supplies
- Needles and syringes
- 0.9% sodium chloride solution or other appropriate fluid
- Oral airway and intubation supplies
- Oxygen supplies
- Portable or wall suction
- PPE
  - For isolation precautions: gloves and PPE, as indicated
  - For antineoplastic administration: double chemotherapy-tested gloves, eye protection, face shield, impervious chemotherapy-resistant gown with long sleeves that closes in the back, and respirator
- Pulse oximeter
- Sphygmomanometer
- Stethoscope

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