Over the past two decades, immunotherapy has emerged as a promising treatment option for patients with cancer. However, newer versions of immunotherapy, such as checkpoint inhibitors, may be associated with unusual adverse effects (AEs) that can range in severity from mild to life-threatening. Unlike common AEs of conventional chemotherapy, which have a predictable nadir or cyclic pattern after administration, AEs of these newer immunotherapies are variable, depending on the type of immunotherapy, route of administration, and mechanism of action. The onset and resolution of these AEs may be present at any time, during administration of treatment, a few weeks after administration of treatment, or several months after completion of treatment. Therefore, improving outcomes in patients undergoing oncologic immunotherapy requires oncology nurses’ knowledge and understanding of various immunotherapy agents, as well as early recognition and management of potential AEs, especially AEs associated with checkpoint inhibitors and other therapies that manipulate T-cell activation causing autoimmune toxicity. This article draws upon current evidence from systematic reviews, meta-analyses, and expert consensus guidelines to provide a brief overview of common immunotherapies used in cancer and management of their associated AEs.

Key words: Adverse events, cancer, immunotherapy, management

Introduction
Over the past two decades, the Food and Drug Administration (FDA) has approved several different types of immunotherapies as treatment options for patients with cancer, secondary to reports of improved survival, and complete remissions in some cancers.[1-7] Immunotherapy uses the body’s immune system to combat cancer; specifically, it stimulates the production of specific antibodies or counteracts malignant cells’ production of signals or pathways that suppress immune responses.[6] However, stimulating the immune system may cause unusual adverse events (AEs), especially with checkpoint inhibitors...
and other therapies that manipulate T-cell activation causing autoimmune toxicity. Occurring in any system of the body, these AEs range from mild to life-threatening in severity, depending on the type of immunotherapy, route of administration, and mechanism of action. Unlike the AEs of conventional chemotherapy, which have a predictable nadir or cyclic pattern after administration, AEs related to these newer versions of immunotherapy are variable in regard to their onset and resolution and may be present at any time, from a period of a few weeks during administration of treatment to several months after completion of treatment. Therefore, improving outcomes in patients undergoing oncologic immunotherapy requires oncology nurses’ knowledge and understanding of the various immunotherapy agents, as well as early recognition and management of potential AEs, especially AEs associated with checkpoint inhibitors and other agents that manipulate T-cell activation causing autoimmune toxicity. This article draws upon current evidence from systemic reviews, meta-analyses, and expert consensus guidelines to provide a brief overview of common immunotherapies used in cancer and management of their associated AEs.

Categories of Immunotherapy

The major oncologic immunotherapies involve cancer vaccines, monoclonal antibodies (mAbs), chimeric antigen receptor (CAR) T-cell therapy, cytokines, oncolytic viral immunotherapy, and immune checkpoint inhibitors. Given the variability in mechanism of action of the different immunotherapies and the heterogeneity of AEs, it is imperative that oncology nurses become familiar with the current version of The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v. 5.0), which is a standardized list of AE terms commonly found in oncology. The CTCAE is available in detail at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. The CTCAE serves as a universal tool for oncology nurses to properly gauge or measure the severity of the AE, track the progress of the AE, document the AEs in standardized terminology, and help oncology nurses to initiate the proper treatment for the AEs based on the CTCAE grade and the established guidelines and algorithms.

Cancer vaccines

Cancer vaccines stimulate or restore the immune system’s ability to target peptides or antigens on cancer cells. Generally, these biological response modifiers are categorized as cell-based, peptide-based, tumor-cell-based, or immune- or dendritic-cell-based vaccines. Currently, sipuleucel-T (Provenge; Dendreon Pharmaceuticals) is the only therapeutic dendritic-cell-based vaccine that has received FDA approval for the treatment of hormone-refractory prostate cancer. Sipuleucel-T uses the patient’s own cells to induce an immune response against prostate acid phosphatase (PAP), which is found in 95% of prostate adenocarcinomas and is specific to prostate tissue. Sipuleucel-T is made by harvesting the patient’s peripheral blood mononuclear cells using leukapheresis. The cells are then sent to the laboratory, where they are cultured in vitro for 36–44 h with a fusion protein, composed of recombinant PAP and granulocyte-macrophage-colony-stimulating factor (GM-CSF), and then reinfused back into the patient. Normally, this process is replicated every 2 weeks for a total of three doses.

Generally, sipuleucel-T is well tolerated; however, common AEs experienced by patients participating in sipuleucel-T clinical trials include chills (44.0%–57.8%), pyrexia (29.3%–36.2%), headache (16.0%–23.3%), myalgia (9.8%–21.6%), influenza-like illness (9.8%–13.8%), and hypertension (7.4%–11.2%). One clinical trial reported groin pain (5%), vomiting (10.9%), dyspnea (10.9%), asthenia (5.3%–14.3%), and hyperhidrosis. Other reported AEs include stroke, myocardial infarction, and increased risk of deep vein thrombosis.

However, most AEs associated with sipuleucel-T are infusion related which are caused by a release of cytokines. Usually, infusion-related AEs are self-limiting and resolve within 24–48 h after vaccine infusion. To minimize infusion-related AEs, the European Society for Medical Oncology clinical practice guidelines recommends premedication with acetaminophen and diphenhydramine and adjustment in the infusion rate of sipuleucel-T [Table 1].

Monoclonal antibodies

mAbs are cell-derived, laboratory-generated substances that target specific antigens on tumors. mAbs – which may be murine (made from mice), chimeric (part mouse and part human), humanized (mouse antibodies attached to human antibodies), or fully human (human antibodies) – hinder tumor growth by inhibiting tumor cells’ survival cascades, interfering with tumor angiogenesis, and enabling malignant cells to avoid programmed cell death (PD) and evade immune checkpoints. To date, the FDA has approved several mAbs for the treatment of cancer [Table 2]. AEs associated with mAbs are specific to the pharmacologic mechanism of action [Table 1], and their management depends on the mechanism of action and the route of administration [Table 1]. For example, mAb-related AEs can range from a mild headache, diarrhea, transient pruritus, and dermatitis to potentially serious or life-threatening AEs such as anaphylaxis, cardiovascular AEs, thromboembolic AEs, cytokine release...
# Table 1: Other Immunotherapy agents

| Immunotherapy agent | Drug and company | Target | Indication | Common selected AEs | Management |
|---------------------|------------------|--------|------------|---------------------|------------|
| CAR T-cell          | Asiabtagene ciloceuc | CD19 | Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. | • Cytokine release syndrome (CSR) (Fever (100.4 °F/38 °C or higher), hypotension, tachycardia, hypoxia, and chills), • Immune effector cell-associated neurotoxicity syndrome (ICANS) (delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, and seizures). | CSR • Grade 1: Supportive care for fever, headache, fatigue, myalgia, and malaise. • Grade 2: Administer tocilizumab intravenously. Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit of 3 doses of tocilizumab in a 24-hour period. Administer corticosteroids if no improvement within 24 h • Grade 3: Give tocilizumab as per grade 2. Administer methylprednisolone 1 mg/kg every 6 hours, continue until the event is grade 1, then taper over 3 days. • Grade 4: Same as per grade 2. Administer methylprednisolone 1000 mg intravenously per day for 3 days. |
|                     | (Yescarta) | | | | |
|                     | KITE Pharma, Inc. | | | | |
| Tisageniecleucel (Kymriah) | Novartis | CD19 | Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. Pediatric and young adults B-cell acute lymphoblastic leukemia. | | |

## Cytokines

| Immunotherapy agent | Drug and company | Target | Indication | Common selected AEs | Management |
|---------------------|------------------|--------|------------|---------------------|------------|
| IFN alpha-2b (Intron A) | Merck | No specific target. Binds to type 1 interferon receptors and activates tyrosine kinase which produces antiproliferative and immunomodulatory effects. | Carcinoid tumors Melanoma Renal cell carcinoma Cutaneous T-cell lymphoma Hairy cell leukemia Follicular lymphoma Chronic myeloid leukemia | • Injection site reaction • Alopecia • Anorexia • Nausea/vomiting • Dry mouth • Increased liver enzymes • Arthralgia • Myalgia • Asthenia • Flu-like symptoms | Assess complete blood counts, thyroid function studies, and liver enzymes. • Assess for depression and suicidal risk. Start antidepressant therapy at the earliest sign of depression. • Assess for autoimmune disorders and discontinue treatment as needed. |
| Aldesleukin (IL-2; Proleukin) | Novartis | No specific target. Inhibits tumor growth by stimulating growth and activity of T cells and B lymphocytes. | Metastatic renal cell carcinoma Metastatic melanoma | • Diarrhea • Chills • Vomiting • Rash • Bilirubinemia • Thrombocytopenia • Nausea • Confusion • Increased serum creatinine | Assess baseline pulmonary, cardiac, hepatic, renal, and neurological function prior to starting treatment. • Monitor for signs and symptoms of infection, treat as needed. • Assess for baseline pre-existing autoimmune disease and inflammatory disorders. • Monitor blood glucose levels throughout treatment. • Monitor vital signs, urine output, and weight. |

Contd...
Table 1: Contd...

| Immunotherapy agent | Drug and company | Target | Indication | Common selected AEs | Management |
|---------------------|------------------|--------|------------|---------------------|------------|
| Vaccine             |                  |        |            |                     |            |
| Sipuleucel-T (Provenge) | Dendreon       | Prostatic acid phosphatase (PAP) | Hormone-refractory prostate cancer | Infusion related reactions • Chills • Fatigue • Fever • Back pain • Nausea • Arthralgias • Headache | Monitor for infusion related reactions. • Consider premedication with acetaminophen and diphenhydramine. • Use universal precautions when handling to limit potential exposure to infectious diseases. |
| Viral therapy       |                  |        |            |                     |            |
| Talimogene laherparepvec (Imlygic or T-VEC) | Angen | No specific target. Designed to mediate tumor regression via replication within and lysis of tumor cells | Advanced melanoma | Fever and chills • Fatigue • Nausea • Flu-like symptoms • Injection site reaction (pain, erythema, swelling) | Assess for injection site reaction. Consider premedication with acetaminophen or indomethacin. Monitor for signs and symptoms of infection, treat as needed. |

syndrome (CRS), hepatitis, pulmonary AEs, hemorrhage, and cytopenias.\[30,34\] While the mechanism behind some mAbs AEs such as cytopenias is unclear, AEs such as Stevens–Johnson syndrome, urticaria, serum sickness, and anaphylaxis are generally mediated by the immune system.\[33\] The mechanism behind pulmonary AEs such as interstitial pneumonitis, acute respiratory distress syndrome, hypersensitivity pneumonitis, or bronchiolitis obliterans organizing pneumonia is a result of activation of cytotoxic T-lymphocytes, which leads to alveolar and vascular damage, cytokine release, and likely cross-reaction between lung and tumor antigens.\[33\] In contrast, cardiac AEs are believed to result from the inhibition of a growth factor (neuregulin 1) which is needed for cardiac development and maintenance.\[33\] Similarly, AE such as acneiform rash which occurs in 50%–100% of patients receiving cetuximab and panitumumab is a result of the inhibition of epidermal growth factor receptor (EGFR) which initiates the alteration and rupture of the epithelial barrier, which in turn facilitates bacterial access and proliferation.\[33\] AEs (hypertension, hemorrhage, and thromboembolism) associated with mAbs that target vascular endothelial growth factor (VEGF) and VEGF receptor are a result of the disruption of physiological processes involved in wound healing, blood pressure regulation, coagulation, renal filtration, and vascular homeostasis.\[31\]

Other frequently reported AEs of mAbs are infusion related and a result of antigen–antibody interactions precipitating cytokine release.\[17,30\] Infusion-related AEs can occur within 30 min to 2 h after the infusion or 24 h later and are described as pruritus, chills, fever, asthenia, dyspnea, nausea, rash, or headache.\[30,34\] Severe and potentially fatal infusion-related AEs may occur in 0.3% of patients and present as angioedema, hypotension, bronchospasm, and cardiac arrest.\[30,34\] Furthermore, the incidence of infusion-related AEs varies among different mAbs. For example, rituximab is 77%, trastuzumab is 40%, cetuximab is 15%–20%, bevacizumab is <3%, and panitumumab is 3%.\[33\] Management of infusion-related AEs is based on well-established clinical practice guidelines by the European Society for Medical Oncology.\[17\]

**Chimeric antigen receptor T-cells**

CAR T-cells are genetically engineered T-cells reprogrammed to produce CARs on the cell membrane.\[8,35\] Once these cells have been collected from the patient’s blood, reprogrammed, and injected back into the patient, tumor-specific recognition occurs, and then, T-cell memory enables the T-cells to proliferate, destroy tumor cells, and
### Table 2: Monoclonal antibodies (mAbs)

| Monoclonal antibodies (mAbs) | Company     | Target | Indication                                                                 | Common selected AEs                                                                 | Management                                                                                                                                 |
|------------------------------|-------------|--------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Bevacizumab (Avastin)        | Genentech   | VEGF   | Metastatic colorectal cancer Non-small cell lung cancer Renal cell cancer Cervical, ovarian, fallopian tube, and peritoneal cancer Recurrent glioblastoma | Epistaxis Headache Hypertension Rhinitis Proteinuria Taste alteration Dry skin Rectal hemorrhage Lacrimation disorder Back pain Exfoliative dermatitis | Hypertension  
  • Evaluate risk and maintain blood pressure within normal range.  
  • Treat with angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, and diuretics.  
  Proteinuria  
  • Assess urinary protein excretion assessment before every cycle of anti-VEGF using a urine dipstick.  
  • If urine dipstick >2+, order 24-h urine collection for protein.  
  • Hold treatment if 24-hour urine protein levels are >2 grams and restart treatment when levels are <2 grams.  
  • Discontinue treatment for 24-hour urine protein >3.5 grams.  
  • Angiotensin II receptors and ACE inhibitors may reduce the severity of proteinuria and end-stage renal disease.  
  Hemorrhage  
  • Prior to starting an anti-VEGF, assess for risk factors or any signs of bleeding.  
  Wound healing  
  • Discontinue treatment at least 28 days prior to surgery and reinitiate at 28 days after surgery or when wound is completely healed.  
  Infection  
  • Assess for signs and symptoms of infection.  
  • Monitor for signs and symptoms of neurotoxic AEs.  
  • Assess infusion related AEs  
  • Pre-medicate with dexamethasone.  |
| Blinatumomab (Blincyto)      | Amgen       | CD19   | Philadelphia-chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia | Infection Headache Neutropenia, Thrombocytopenia Fever Anemia Infusion reaction | Electrolytes  
  • Monitor electrolyte imbalances (magnesium, calcium, potassium) and replete as needed.  
  Treatment of cutaneous AEs  
  • Rash  
  • Grade 1- Apply emollients regularly.  
  • Grade 2- Oral or topical application of tetracycline antibiotics, corticosteroids, moisturizers, and sunscreen.  
  Refer to dermatologist.  
  • Grade 3- Continue topical and oral regimen and refer to dermatologist. Hold EGFR therapy.  
  Paronychia  
  • Grade 1- Warm water or white vinegar soaks.  
  • Grade 2- Topical corticosteroids and antimicrobials, consult a dermatologist and podiatrist as needed.  
  • Grade 3- Refer to dermatologist or podiatrist, continue topical steroids, antifungals, antibiotics, antiseptics, and silver nitrate.  
  Gastrointestinal AEs  
  • Diarrhea  
  • Assess for infection versus drug related.  
  • Grade 1-2- loperamide, hydrate.  
  • Grade 3-4- In addition to loperamide, add codeine for a short-term basis.  
  • Obtain stool cultures and hospitalization for intravenous fluids as needed.  
  • Referral to gastroenterologist if diarrhea does not resolve.  |
| Brentuximab vedotin (Adcetris) | SeattleGenetics | CD30  | Hodgkin lymphoma Systemic anaplastic large cell lymphoma | Neutropenia Peripheral sensory neuropathy Fatigue Nausea/vomiting Anemia Upper respiratory infection Diarrhea Pyrexia Rash Thrombocytopenia Cough |  |
| Cetuximab (Erbitux)          | Lilly       | EGFR   | Metastatic colorectal cancer Head and neck cancer | Acne-like rash Fatigue Growth of eyelashes Dry skin Allergic reaction, Myocardial infarction Diarrhea Hypomagnesemia Paronychia |  |
| Monoclonal antibodies (mAbs) | Company | Target | Indication | Common selected AEs | Management |
|----------------------------|---------|--------|------------|---------------------|------------|
| Daratumumab (Darzalex)     | Janssen | CD38   | Multiple myeloma | Fatigue, Nausea/vomiting, Diarrhea, Constipation, Muscle spasms, Back pain, Fever, chills, Dizziness, Insomnia, Dyspnea, Cough, Edema, Neuropathy, Arthralgias, Cold-like symptoms | Fatigue • Assess treatable contributing factors. • Assess psychosocial factors. • Treatment may include physical activity, psychosocial interventions, mind-body interventions, and pharmacologic interventions. • Assess for signs and symptoms of infection. |
| Dinutuximab (Unituxin)      | United Therapeutics | GD2 gangloside | Neuroblastoma (in children) | Pain, Fever, Thrombocytopenia, Lymphopenia, Infusion reactions, Hypotension, Hypertension, Hyponatremia | • Assess for signs and symptoms of infection. • Monitor blood pressure and treat as per guidelines. Discontinue treatment for severe or uncontrolled hypertension. • Assess infusion related AEs. |
| Elotuzumab (Empliciti)      | Bristol-Myers Squibb | SLAMF7 | Multiple myeloma | Infusion reaction, Hypertension | • Assess for signs and symptoms of infection. • Monitor blood pressure and treat as per guidelines. Discontinue treatment for severe or uncontrolled hypertension. • Assess infusion related AEs. |
| Gentuzumab Ozogamicin (Mylotarg) | Pfizer Inc. | CD33 | Newly-Diagnosed Acute myeloid leukemia (AML), Relapsed or refractory AML | Nausea/vomiting, Diarrhea, Constipation, Headache, Dizziness, Anxiety, Depression, Cytopenia, Elevated liver enzymes | • Assess for signs and symptoms of infection. • Assess complete blood counts and metabolic panels three times per week. • Assess for signs and symptoms of infection. • Assess infusion related AEs. Discontinue for severe infusion reactions. |
| Ibritumomab tiuxetan (Zevalin) | Biogen Idec, Inc | CD20 | Non-Hodgkin lymphoma | Cytopenia, Fatigue, Nasopharyngitis, Nausea, Abdominal pain, Asthenia, Cough, Diarrhea, Pyrexia | • Assess for signs and symptoms of infection. • Assess infusion related AEs. Discontinue for severe infusion reactions. • Monitor complete blood counts and platelet count weekly after administration of drug. |
| Necitumumab (Portrazza)    | Lilly   | EGFR  | Non-small cell lung cancer | Hypomagnesemia, Hypokalemia, Vomiting, Diarrhea, Acne, Weight loss, Mucositis, Hemoptysis | Electrolytes • Monitor electrolyte imbalances (magnesium, calcium, potassium) and replete as needed. Treatment of cutaneous AEs • Rash ✗ Grade 1- Apply emollients regularly. ✗ Grade 2- Oral or topical application of tetracycline antibiotics, corticosteroids, moisturizers, and sunscreen. Refer to dermatologist. ✗ Grade 3- Continue topical and oral regimen and refer to dermatologist. Hold EGFR therapy. • Paronychia ✗ Grade 1- Warm water or white vinegar soaks. ✗ Grade 2- Topical corticosteroids and antimicrobials, consult a dermatologist and podiatrist as needed. ✗ Grade 3- Refer to dermatologist or podiatrist, continue topical steroids, antifungals, antibiotics, antiseptics, and silver nitrate. |

Contd...
| Monoclonal antibodies (mAbs) | Company       | Target | Indication                          | Common selected AEs                                                                 | Management                                                                                                                                 |
|----------------------------|---------------|--------|-------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Obinutuzumab (Gazyva)      | Genentech     | CD20   | Chronic myeloid leukemia            | Infusion reaction                                                                   | • Monitor for infusion related AEs and treat as per guidelines.                        |
|                            |               |        | Follicular lymphoma                 | Neutropenia                                                                         | • Monitor for signs and symptoms of infection.                                          |
|                            |               |        |                                     | Thrombocytopenia, Anemia                                                           | • Monitor complete blood counts frequently.                                             |
|                            |               |        |                                     | Fever                                                                               |                                                                                                                                          |
|                            |               |        |                                     | Cough                                                                               |                                                                                                                                          |
|                            |               |        |                                     | Diarrhea                                                                            |                                                                                                                                          |
|                            |               |        |                                     | Nausea                                                                              |                                                                                                                                          |
|                            |               |        |                                     | Fatigue                                                                             |                                                                                                                                          |
|                            |               |        |                                     | Dyspnea                                                                             |                                                                                                                                          |
|                            |               |        |                                     | Rash                                                                                |                                                                                                                                          |
|                            |               |        |                                     | Nausea                                                                              |                                                                                                                                          |
|                            |               |        |                                     | Bronchitis                                                                          |                                                                                                                                          |
|                            |               |        |                                     | Upper respiratory tract infection                                                  |                                                                                                                                          |
| Ofatumumab (Arzerra)       | Novartis      | CD20   | Chronic lymphocytic leukemia        | Infusion reaction                                                                   | • Pre-medicate with oral or intravenous antihistamine, acetaminophen, and intravenous corticosteroid to minimize infusion reaction.          |
|                            |               |        |                                     | Neutropenia                                                                         | • Monitor complete blood counts and assess neurologic function.                                                                       |
|                            |               |        |                                     | Pneumonia                                                                           |                                                                                                                                          |
|                            |               |        |                                     | Fever                                                                               |                                                                                                                                          |
|                            |               |        |                                     | Cough                                                                               |                                                                                                                                          |
|                            |               |        |                                     | Diarrhea                                                                            |                                                                                                                                          |
|                            |               |        |                                     | Anemia                                                                              |                                                                                                                                          |
|                            |               |        |                                     | Fatigue                                                                             |                                                                                                                                          |
|                            |               |        |                                     | Dyspnea                                                                             |                                                                                                                                          |
|                            |               |        |                                     | Rash                                                                                |                                                                                                                                          |
|                            |               |        |                                     | Nausea                                                                              |                                                                                                                                          |
|                            |               |        |                                     | Bronchitis                                                                          |                                                                                                                                          |
| Olaratumab (Lartruvo)      | Lilly         | PDGF R | Soft tissue sarcoma                 | Nausea/vomiting                                                                     | • Monitor electrolyte imbalances and replete as needed.                                |
|                            |               | alpha  |                                     | Fatigue                                                                             | • Monitor for signs and symptoms of infection.                                          |
|                            |               |        |                                     | Myalgias                                                                            | • Monitor complete blood counts frequently.                                           |
|                            |               |        |                                     | Mucositis                                                                           | • Monitor for infusion related AEs and treat as per guidelines.                                                                       |
|                            |               |        |                                     | Alopecia                                                                            |                                                                                                                                          |
|                            |               |        |                                     | Diarrhea                                                                            |                                                                                                                                          |
|                            |               |        |                                     | Anorexia                                                                            |                                                                                                                                          |
|                            |               |        |                                     | Abdominal pain                                                                      |                                                                                                                                          |
|                            |               |        |                                     | Neuropathy                                                                          |                                                                                                                                          |
|                            |               |        |                                     | Headache                                                                           |                                                                                                                                          |
|                            |               |        |                                     | Lymphopenia                                                                         |                                                                                                                                          |
|                            |               |        |                                     | Neutropenia                                                                          |                                                                                                                                          |
|                            |               |        |                                     | Thrombocytopenia                                                                    |                                                                                                                                          |
|                            |               |        |                                     | Hyperglycemia                                                                       |                                                                                                                                          |
|                            |               |        |                                     | Elevated activated Partial thromboplastin time                                      |                                                                                                                                          |
|                            |               |        |                                     | Hypokalemia                                                                         |                                                                                                                                          |
|                            |               |        |                                     | Hypophosphatemia                                                                    |                                                                                                                                          |
| Panitumumab (Vectibix)     | Amgen         | EGFR   | Wild-type RAS metastatic colorectal cancer | Acneiform dermatitis                                                               | Electrolytes Monitor electrolyte imbalances (magnesium, calcium, potassium) and replete as needed.                                      |
|                            |               |        |                                     | Pruritus                                                                            | Treatment of cutaneous AEs.                                                           |
|                            |               |        |                                     | Rash                                                                                | • Rash                                                                               |
|                            |               |        |                                     | Skin exfoliation                                                                    | • Grade 1- Apply emollients regularly.                                                 |
|                            |               |        |                                     | Paronychia                                                                          | • Grade 2- Oral or topical application of tetracycline antibiotics, corticosteroids, moisturizers, and sunscreen. Refer to dermatologist.|
|                            |               |        |                                     | Dry skin                                                                            | • Grade 3- Continue topical and oral regimen and refer to dermatologist. Hold EGFR therapy.                                             |
|                            |               |        |                                     | Skin rashes                                                                         |                                                                                                                                          |
|                            |               |        |                                     | Diarrhea, Nausea/vomiting                                                           |                                                                                                                                          |
|                            |               |        |                                     | Fatigue                                                                             |                                                                                                                                          |
|                            |               |        |                                     | Abdominal pain                                                                      |                                                                                                                                          |
|                            |               |        |                                     | Overgrowth of eyelashes                                                            |                                                                                                                                          |
### Table 2: Contd...

| Monoclonal antibodies (mAbs) | Company | Target | Indication | Common selected AEs | Management |
|------------------------------|---------|--------|------------|---------------------|------------|
| **Pertuzumab (Perjeta)**    | Genentech | HER-2  | Metastatic breast cancer | Nausea | • Paronychia  
  ✓ Grade 1- Warm water or white vinegar soaks.  
  ✓ Grade 2- Topical corticosteroids and antimicrobials, consult a dermatologist and podiatrist as needed.  
  ✓ Grade 3- Refer to dermatologist or podiatrist, continue topical steroids, antifungals, antibiotics, antiseptics, and silver nitrate.  
  • Gastrointestinal AEs  
  ✓ Diarrhea  
  ✓ Assess for infection versus drug related.  
  ✓ Grade 1-2- loperamide, hydrate.  
  ✓ Grade 3-4- In addition to loperamide, add codeine for a short-term basis.  
  ✓ Obtain stool cultures and hospitalization for intravenous fluids as needed.  
  ✓ Referral to gastroenterologist if diarrhea does not resolve. |
| **Ramucirumab (Cyramza)**   | Agen   | VEGFR2 | Non-small cell lung cancer | Hypertension | • Hypertension  
  ✓ Evaluate risk and maintain blood pressure within normal range.  
  ✓ Treat with angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, and diuretics.  
  • Discontinue treatment for severe or uncontrolled hypertension.  
  • Hemorrhage  
  ✓ Prior to starting an anti-VEGF, assess for risk factors or any signs of bleeding.  
  • Proteinuria  
  ✓ Assess urine protein levels protein levels before each cycle.  
  • Assess for infusion related AEs  
  • Premedicate with acetaminophen and antihistamine prior to each infusion.  
  • Assess complete blood counts and renal function. |
| **Rituxin (Rituximab)**     | Genentech | CD20  | Low grade or follicular lymphoma | Infusion reactions | • Assess for signs and symptoms of infection.  
  • Assess left ventricular ejection function and monitor for cardiac failure or dysfunction. |
| **Trastuzumab (Herceptin)** | Roche  | HER-2  | Adjuvant and Metastatic breast cancer | Fever | • Assess liver enzymes at baseline and prior to each dose.  
  • Monitor electrolytes and replete as needed.  
  • Monitor for signs and symptoms of infection.  
  • Assess left ventricular function at baseline and during treatment.  
  • Monitor complete blood counts frequently. |
| **Trastuzumab Emtrastine (Kadcyla)** | Genentech | HER-2  | Metastatic breast cancer | Nausea | • Thrombocytopenia  
  • Elevated liver enzymes  
  • Hypokalemia  
  • Myalgia  
  • Arthralgia  
  • Anemia  
  • Neutropenia  
  • Fatigue  
  • Nausea  
  • Cardiomyopathy |
A common AE associated with CAR T-cell therapy is CRS, with incidence rates of 43%–100% in adult and pediatric patients with relapsed and refractory acute lymphoblastic leukemia.\(^{[18,38-40]}\) CSR occurs when T-cells engage with a target antigen, multiply in the body, and release cytokines that cause an inflammatory response.\(^{[18]}\) The onset and severity of CRS depend on the type of CAR T-cell therapy and the degree of immune cell activation.\(^{[19]}\) Typically, CRS symptoms, if they occur, develop days to weeks after infusion of CAR T-cell therapy.\(^{[19]}\) Patients with CRS may experience constitutional symptoms such as fever, rigors, malaise, myalgias, arthralgias, fatigue, nausea, vomiting, and headache, while other patients may develop severe symptoms such as hypotension, tachycardia, capillary leak syndrome, and multiorgan dysfunction.\(^{[18,19,38-41]}\) In addition, patients may experience neurotoxicity, also known as immune effector cell-associated neurotoxicity syndrome, which can occur concurrently with or after CSR, and vary from mild, expressive aphasia to confusion, lethargy, agitation, delirium, difficulty concentrating, seizures, encephalopathy, and infrequently, cerebral edema.\(^{[19,42]}\)

In a trial conducted by Schuster et al., in which 28 patients with diffuse large B-cell lymphoma or follicular lymphoma that had relapsed or was refractory to previous treatment were treated with CAR T-cell therapy, CRS occurred in 16 patients and neurotoxicity (ranging from mild cognitive disturbance to global encephalopathy) occurred in 11 patients.\(^{[42]}\) In this study, CRS and neurotoxicity were self-limiting in all patients but one, who was given tocilizumab (Actemra: Genentech, South San Francisco, CA, USA), an anti-interleukin (IL)-6 antibody that reversed the symptoms of CRS within a few hours.\(^{[42]}\) A similar study of 161 patients (133 patients completed the toxicity assessment) with acute lymphoblastic leukemia, chronic lymphocytic leukemia, and non-Hodgkin's lymphoma treated with CAR T-cell therapy reported that CRS developed in 71% of patients and that neurotoxicity was observed in 40% of patients.\(^{[43]}\) In this study, CRS and neurotoxicity were reversible except six patients who died.\(^{[43]}\)

Management of CRS depends on the grading as outlined in consensus guidelines established by a CAR T-cell therapy-associated toxicity working group and the American Society for Blood and Marrow Transplant [Table 1].\(^{[20,44]}\) Opinions vary on the need for hospitalization; Neelapu et al. recommended hospitalization and close monitoring of patients for a period of 7 days after CAR T-cell infusion, whereas Teachey et al. posited that patients can receive CAR T-cells in the outpatient setting and be admitted to the hospital only if the patient develops a fever.\(^{[20,45]}\)

**Cytokines**

Cytokines, which are small protein molecules naturally produced by the body, regulate the differentiation, migration, activation, and suppression of leukocytes.\(^{[13]}\) Of the several different varieties of cytokines, recombinant interferon alpha-2b (IFN-alpha-2b) and IL-2 are the most widely used cytokines in cancer treatment.\(^{[21]}\) Recombinant IFN-alpha-2b has been approved for non-Hodgkin's lymphoma, hairy cell leukemia, and melanoma.\(^{[46]}\) Recombinant IFN-alpha-2b is associated with flu-like symptoms, such as chills, fever, headache, and myalgia,\(^{[10,22]}\) which are generally controlled with nonsteroidal anti-inflammatory drugs.\(^{[47]}\) Other potential AEs include anorexia, depression, fatigue, hepatic dysfunction, thyroid dysfunction, autoimmune hemolytic anemia/thrombocytopenia, and immune-mediated nephritict syndrome.\(^{[10,48]}\) Patients with grade 2–3 fatigue may require a break from treatment or a dose reduction, and patients with depression may require prophylactic antidepressants.\(^{[47]}\) Generally, AEs associated with IFN-alpha-2b tend to reverse rapidly when therapy is discontinued.\(^{[10]}\)

IL-2 is a T-cell growth factor that promotes the antitumor activity of natural killer cells, enhances the growth and proliferation of regulatory T-cells (Tregs), and induces lymphokine-activated killer cells that mediate antitumor effects.\(^{[13]}\) IL-2 has been approved for the treatment of metastatic melanoma and metastatic renal cell cancer and can be administered intravenously or subcutaneously.\(^{[49]}\) Common AEs associated with IL-2 include chills, fatigue, fever, nausea, diarrhea, vomiting, hypotension, transaminitis, dyspnea, oliguria, and hyperbilirubinemia.\(^{[10,23]}\) In a retrospective analysis of 243 patients with advanced melanoma who received high-dose IL-2, the following AEs were reported: oliguria (14%–58%), hypotension (14%–39%), and tachycardia (10%–21%).\(^{[50]}\) Given that these AEs can be severe or life-threatening, most patients are administered high-dose IL-2 on an inpatient unit with cardiac monitoring at institutions that have healthcare providers who have experience in recognizing and managing these AEs using specific institutional guidelines and standing orders [Table 1].\(^{[10,23,44]}\)

**Oncolytic viral therapy**

Oncolytic viral therapy, which increases a patient’s immune response to cancer without harming normal
| Checkpoint inhibitors | Company | Target | Indication | Common selected irAEs | Management |
|-----------------------|---------|--------|------------|-----------------------|------------|
| Atezolizumab (Tecentriq) | Roche/Genentech Ltd | PD-L1 | Metastatic nonsmall cell lung cancer | Fatigue | Baseline |
|                       |         |        | Advanced urothelial cancer | Diarrhea, Fever, Myalgias | Perform a baseline assessment of thyroid studies, complete blood counts, liver function, and metabolic panels, and document them prior to starting each treatment and at intervals of 6-12 weeks for the first 6 months after completing treatment |
|                       |         |        | | Hepatitis | Document any co-morbid conditions |
|                       |         |        | | Pneumonitis | Evaluate baseline radiological examinations |
|                       |         |        | | Dermatitis | Assess for history of autoimmune disease, which may worsen with starting a checkpoint inhibitor |
|                       |         |        | | | Inform patients and caregivers of potential irAEs before treatment initiation |
|                       |         |        | | Infusion irAEs | Infusion irAEs |
| Avelumab (Ravencio)   | Merck  | PD-L1 | Metastatic Merkel cell cancer | Fatigue, Myalgias, Colitis | Assess for infusion related AEs |
|                       |         |        | | Infusion reaction | Interrupt or slow the rate of infusion for grade 1 or 2 |
|                       |         |        | | Dermatitis, Hypothyroidism, Hyperthyroidism, Hyperglycemia, Nephritis, Hepatitis | For grade 3 or 4, permanently, discontinue the treatment |
|                       |         |        | | | General management |
|                       |         |        | | | Assess for irAEs and manage according to grade, clinical guidelines or algorithms |
|                       |         |        | | | Fatigue irAEs |
|                       |         |        | | | Assess adenocorticotropic hormone, cortisol, and testosterone |
|                       |         |        | | | Assess treatable contributing factors (gastrointestinal, hepatic, and pulmonary irAEs) |
|                       |         |        | | | Assess psychosocial factors |
|                       |         |        | | | Treatment may include physical activity, psychosocial interventions, mind-body interventions, and pharmacologic interventions |
| Durvalumab (Imfinzi)  | AstraZeneca | PD-L1 | Unresectable stage III non-small cell lung cancer | Fatigue | Dermatologic irAEs |
|                       |         |        | Urothelial cancer | Colitis, Fever, Myalgias | Grade 1- Treat with topical emollients, oral antihistamines, and mild strength topical corticosteroids |
|                       |         |        | | | Grade 2- Topical emollients, oral antihistamines, median to high strength topical steroids |
|                       |         |        | | | Grade 3- Hold treatment, treat with topical emollients, oral antihistamines, high strength topical steroids or systemic corticosteroids depending on the severity of symptoms |
|                       |         |        | | | Grade 4- Hold treatment, hospital admission, dermatologist referral, intravenous methylprednisolone |
| Ipilimumab (Yervoy)   | Bristol-Myers Squibb Co | CTLA-4 | Melanoma | Fatigue, Diarrhea, Colitis | Gastrointestinal irAEs |
|                       |         |        | Combined with Nivolumab for treatment of advanced renal cell cancer, and microsatellite instability high or mismatch repair deficient metastatic colorectal cancer | Myalgias | Assess complete blood count, serum electrolyte panel, stool analysis for enteropathogens, and Clostridium difficile |
|                       |         |        | | | Grade 1- Consider holding treatment, hydration, loperamide |
|                       |         |        | | | Grade 2- Hold treatment, intravenous methylprednisolone, consider infliximab if no response to steroids. If refractory to infliximab, consider vedolizumab |
|                       |         |        | | | Grade 3- Discontinue anti-CTLA-4, consider resuming anti-PD1/anti-PD-L1 after symptoms have resolved. Consider Gastrointestinal referral |
|                       |         |        | | | Grade 4- Discontinue treatment permanently, hospitalization |
| Nivolumab (Opdivo)    | Bristol-Myers Squibb Co | PD-1 | Metastatic melanoma | Fatigue | Endocrine irAEs |
|                       |         |        | Metastatic non-small cell lung cancer | Myalgias | Thyroid |
|                       |         |        | Advanced renal cell cancer | Dermatitis | 1. Check thyroid panel at baseline and prior to each treatment |
|                       |         |        | Metastatic urachial cancer | Diarrhea | 2. Hormone replacement therapy for symptomatic hypothyroidism or TSH > 10 |
|                       |         |        | Classical Hodgkin lymphoma | Hypothyroidism | 3. Beta-blockers for symptomatic hyperthyroidism |
|                       |         |        | Recurrent/metastatic squamous cell cancer of the head and neck | Colitis, Hepatitis, Pneumonitis | Diabetes mellitus |
|                       |         |        | Hapatocellular cancer | | Monitor blood glucose levels with each dose |
|                       |         |        | | | Lifestyle and diet modification as needed |
|                       |         |        | | | Endocrine referral if symptomatic or uncontrolled blood glucose levels |
| Pembrolizumab (Keytruda) | Merck and Co Inc | PD-1 | Advanced non-small cell lung cancer | Fatigue | Hepatic irAEs |
|                       |         |        | Classical Hodgkin lymphoma | Dermatitis | Evaluate liver function tests prior to starting every cycle of treatment |
|                       |         |        | Advanced gastric cancer | Arthralgias | Grade 2- Hold treatment, monitor liver function tests twice weekly |
|                       |         |        | | | If grade 2 lasts longer than 1-2 weeks, check for disease related causes, concomitant drug or alcohol administration, and infectious diseases |
|                       |         |        | Advanced melanoma | Cough | Treat with corticosteroids |
|                       |         |        | Microsatellite instability-High cancer | Hyperglycemia | |
|                       |         |        | Advanced cervical cancer | Hepatitis | |
|                       |         |        | Head and neck squamous cell cancer | Pruritus | |
tissue, uses a modified virus that can force tumor cells to self-destruct and release antigens. In 2015, talimogene laherparepvec (T-VEC) (Imlygic: Amgen, Thousand Oaks, CA, USA), a second-generation oncolytic herpes simplex type 1, was engineered to express human GM-CSF, received FDA approval for use in patients with advanced melanoma. The mechanism of action of T-VEC is unknown; however, it is thought that T-VEC uses the herpes virus entry mediator, glycoproteins, and nectins on the cell surface to enter cancer cells and trigger cell lysis. Common AEs associated with T-VEC are fever (42.8%), chills (48.6%), fatigue (50.3%), nausea (35.6%), vomiting (21.2%), headache (18.8%), and erythema, pain, and cellulitis (27.7%) at the injection site. Management of AEs is mainly supportive; for example, acetaminophen or indomethacin can be given for pain, chills, or fever, and ice bags can be applied to the injection site 5–10 min before T-VEC injection to minimize pain at the injection site [Table 1].

**Immune checkpoint inhibitors**

Immune checkpoint inhibitors, which enhance the immune system’s preexisting antitumor responses, target molecules that switch immune responses on and off. For instance, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is normally expressed on the surface of naive effector T-cells and Tregs, which inhibit autoimmunity, and promotes tolerance to self-antigens. Similarly, PD-1 is an immune inhibitory receptor which negatively regulates T-cell functions through the engagement of programmed death ligand 1 (PD-L1), which is found on various malignant cells. Hence, checkpoint inhibitors disrupt the signaling pathways that allow cancer cells to evade T-cell-mediated death by preventing CTLA-4 and PD-1 from binding with specific ligands, thus enhancing the immune system’s ability to attack malignant cells. The FDA has approved several checkpoint inhibitors that have shown clinical efficacy in the treatment of a number of cancers [Table 3].

The AEs associated with checkpoint inhibitors are referred to as immune-related AEs (irAEs). These irAEs are secondary to the infiltration of activated T-cells – which are also involved in autoimmunity – into normal tissue. These irAEs can affect any organ or multiple organs simultaneously or at different time points. The areas most commonly affected are skin, gastrointestinal tract, endocrine, lungs, thyroid, pituitary, adrenal glands, and musculoskeletal system and less commonly affected are nervous, renal, hematologic, ocular, and cardiovascular system. For example, in a retrospective study of 50 patients with nonsmall cell lung cancer, who were treated with an immune checkpoint inhibitor, the

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**Table 3: Contd...**

| Checkpoint inhibitors | Company | Target | Indication |
|-----------------------|---------|--------|------------|
| Ipilimumab (CTLA-4)   | Bristol-Myers Squibb | Advanced melanoma, urothelial bladder cancer, primary mediastinal B-cell lymphoma | |
| Nivolumab (PD-1)      | Merck   | Lung, melanoma, head and neck, renal cell, bladder, esophageal | |
| Pembrolizumab (PD-1)  | Merck   | Lung, melanoma, head and neck, esophageal, bladder, head and neck, renal cell, | |
most frequent irAEs were fatigue (42%), rash (22%), nausea (20%), and fever (20%). Similarly, a retrospective analysis to assess the safety profile of nivolumab in 576 patients with advanced melanoma found that 71% of patients experienced irAEs, with the most common irAEs being fatigue (25%), pruritus (17%), diarrhea (13%), and rash (13%).

The management of irAEs is based on well-established clinical practice guidelines, such as the National Comprehensive Cancer Network, the American Society of Clinical Oncology, the European Society for Medical Oncology, and the Society for Immunotherapy of Cancer. For patients with grade 1 irAEs that are not cardiac, hematologic, or neurologically related, they continue checkpoint inhibitors with close monitoring. For patients with grade 2 irAEs, the checkpoint inhibitor should be put on hold and corticosteroids may be given; the checkpoint inhibitor may be resumed when the patient’s symptoms and/or laboratory values return to grade 1 or less. For patients with grade 3 irAEs, the checkpoint inhibitor should be placed on hold and high-dose corticosteroids should be administered and tapered over 4–6 weeks; if symptoms do not improve within 48–72 h, administer infliximab; however, if symptoms and/or laboratory values return to grade 1 or less, the checkpoint inhibitor may be resumed with caution. For patients with grade 4 irAEs – except for endocrinopathies that are controlled with hormone replacement – the checkpoint inhibitor should be permanently discontinued.

Since check inhibitors can cause irAEs to occur in any organ of the body, potentiate autoimmune diseases, or aggravate other comorbid diseases, patients should be thoroughly screened and examined before starting an immune checkpoint inhibitor. Furthermore, patients and caregivers should be educated in early recognition and management of irAEs to minimize serious or life-threatening complications. A complete patient educational guide on irAEs can be accessed at https://www.esmo.org/Patients/Patient-Guides/Patient-Guide-on-Immunotherapy-Side-Effects.
**Combination immunotherapy**

Although immunotherapy has changed the landscape of cancer treatment, one of the biggest challenges of this type of treatment is that many patients do not benefit from it (i.e., they have primary resistance) and some patients relapsed after a period of response (i.e., they develop acquired resistance). To overcome this challenge, researchers are using strategies such as combining anti-PD-1 or PD-L1 agents with other immunotherapy agents, molecular targeted therapy, vaccines, chemotherapies, radiotherapy, or chemoradiotherapies. As of September 2017, over 1,105 combination immunotherapy clinical trials were in progress; however, only one checkpoint inhibitor combination, nivolumab (Opdivo) with ipilimumab (Yervoy), has been approved for clinical use.

As checkpoint inhibitors are combined with other immunotherapy agents or other treatment modalities, the likelihood of more severe or newer AEs occurring increases. For example, a systematic review that assessed the clinical, epidemiological, humanistic, and economic burden of gastrointestinal AEs due to combination checkpoint inhibitors in advance melanoma reported that patients who received combination of ipilimumab plus nivolumab experienced more AEs than patients who received monotherapy checkpoint inhibitors. Similarly, an observational study of patients with nonsmall cell lung cancer receiving nivolumab plus an EGFR-tyrosine kinase inhibitor (TKI) reported higher incidents of interstitial pneumonitis for nivolumab in combination with EGFR-TKI versus treatment with either drug alone.

**Conclusion**

Because of the variability in the mechanism of action among the major categories of oncologic immunotherapy treatments, and because of the heterogeneity of AEs, it is imperative that oncology nurses become familiar with the different AEs so that they can initiate appropriate management and referrals to specialist to improve patient outcomes. Oncology nurses need to be on the forefront of assessing and documenting AEs and the long-term impact on patients, which may lead to a better understanding of why some patients develop AEs and how they can be predicted and alleviated in patients with cancer.

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