Review Article

Adverse Events of Oncologic Immunotherapy and Their Management

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ABSTRACT

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.[8] However, stimulating the immune system may cause unusual adverse events (AEs), especially with checkpoint inhibitors

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and other therapies that manipulate T-cell activation causing autoimmune toxicity.[9] Occurring in any system of the body, these AEs range from mild to life-threating in severity, depending on the type of immunotherapy, route of administration, and mechanism of action.[10,11] 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.[12] 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.[11] 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 standardize 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.[13] Generally, these biological response modifiers are categorized as cell-based, peptide-based, tumor-cell-based, or immune- or dendritic-cell-based vaccines.[10] 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.[14] Sipuleucel-T uses the patient's own cells to induce an immune response against prostatic acid phosphatase (PAP), which is found in 95% of prostate adenocarcinomas and is specific to prostate tissue.[15] 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.[14] Normally, this process is replicated every 2 weeks for a total of three doses.[15]

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%).[15] One clinical trial reported groin pain (5%), vomiting (10.9%), dyspnea (10.9%), asthenia (5.3%–14.3%), and hyperhidrosis.[15] Other reported AEs include stroke, myocardial infarction, and increased risk of deep vein thrombosis.[16]

However, most AEs associated with sipuleucel-T are infusion related which are caused by a release of cytokines.[17] Usually, infusion-related AEs are self-limiting and resolve within 24–48 h after vaccine infusion.[10] 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].[15,17-25]

Monoclonal antibodies

mAbs are cell-derived, laboratory-generated substances that target specific antigens on tumors.[8] 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.[26] To date, the FDA has approved several mAbs for the treatment of cancer [Table 2].[17,26-33]

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].[10,26-29] 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					
	Axicabtagene ciloleucel (Yescarta) KITE Pharma, Inc.	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, aphasis, lethargy, difficulty concentrating, agitation, tremor, and seizures). • Neutropenia • Anemia • Fatigue • Anorexia • Diarrhea • Nausea/vomiting • Constipation • Cardiac arrhythmias	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 methylprednisone 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. ICANS • Grade 2 with concurrent CRS. Administer tocilizumab as per grade 2 CRS. If no improvement within 24 hours, start dexamethasone 10 mg every 6 hours until event returns to grade 1. If no concurrent CRS, administer dexamethasone 10 mg every 6 hours until event is grade 1 or less, taper of 3 days. • Grade 3 with concurrent CRS. Administer tocilizumab as per grade 2 CRS, and start dexamethasone with first dose of tocilizumab, repeat dexamethasone every 6 hours until event is grade 1, then taper over 3 days. If no concurrent CRS, administer dexamethasone every 6 hours until grade 1, taper of 3 days. Consider adding prophylaxis non-sedating anti-seizure medication. • Grade 4 with concurrent CRS. Start tocilizumab as per grade 2 CRS and methylprednisolone 1000 mg per day with the first dose of tocilizumab. Continue methylprednisolone for 2 more days. If no concurrent CRS, administer methylprednisolone 1000 mg per day for 3 days. General • Monitor for hypersensitivity reactions during infusion. • Monitor for signs and symptoms of infection, treat as needed. • Monitor complete blood counts frequently. • Encourage patients to avoid driving and engaging in hazardous occupations or activities for at least 8 weeks post treatment.
	Tisagenlecleucel (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					
	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.

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Table 1: Contd...

Immunotherapy agent	Drug and company	Target	Indication	Common selected AEs	Management
				• Capillary leak syndrome (peripheral edema, hypotension, pleural effusion, dyspnea, ascites, oliguria, weight gain, fever, pulmonary edema)	• Assess complete blood counts, electrolytes, renal, and hepatic function daily while receiving treatment. • Treat symptoms with steroids, intravenous immune globulin (IVIG), β2 agonist, and volume replacements as per individual facility guidelines.
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) Amgen	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.
Blinatumomab (Blincyto)	Amgen	CD19	Philadelphia-chromosome -negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia	Infection Headache Neutropenia, Thrombocytopenia Fever Anemia Infusion reaction	• Assess for signs and symptoms of infection. • Monitor for signs and symptoms of neurotoxic AEs. • Assess infusion related AEs • Pre-medicate with dexamethasone.
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	• Assess complete blood count and treat for grade 3 or higher neutropenia. • Assess for signs and symptoms of infection. • Assess and grade peripheral neuropathy and treat as needed.
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	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.

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Table 2: Contd...

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 Fever, chills 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.
Gemtuzumab 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 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.

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Table 2: Contd...

Monoclonal antibodies (mAbs)	Company	Target	Indication	Common selected AEs	Management
					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. • Stomatitis and Mucositis ✓ Grade 1- Continue EGFR, oral rinses, non-alcoholic mouthwashes. Consider prophylaxis with antifungal, antiviral, and antibacterial. ✓ Grade 2- Hold EGFR, topical analgesics, mucosal coating agents, and benzydamine HCL may be administered as needed. Treat infections with topical or systemic antibacterials. ✓ Grade 3- Discontinue EGFR, hospitalization for supportive care.
Obinutuzumab (Gazyva)	Genentech	CD20	Chronic myeloid leukemia Follicular lymphoma	Infusion reaction Neutropenia Thrombocytopenia, Anemia Fever Cough Nausea Diarrhea	• Monitor for infusion related AEs and treat as per guidelines. • Monitor for signs and symptoms of infection. • Monitor complete blood counts frequently.
Ofatumumab (Arzerra)	Novartis	CD20	Chronic lymphocytic leukemia	Infusion reaction Neutropenia Pneumonia Fever Cough Diarrhea Anemia Fatigue Dyspnea Rash Nausea Bronchitis Upper respiratory tract infection	• Pre-medicate with oral or intravenous antihistamine, acetaminophen, and intravenous corticosteroid to minimize infusion reaction. • Monitor complete blood counts and assess neurologic function.
Olaratumab (Lartruvo)	Lilly	PDGF R alpha	Soft tissue sarcoma	Nausea/vomiting Fatigue Myalgias Mucositis Alopecia Diarrhea Anorexia Abdominal pain Neuropathy Headache Lymphopenia Neutropenia Thrombocytopenia Hyperglycemia Elevated activated Partial thromboplastin time Hypokalemia, Hypophosphatemia	• Monitor electrolyte imbalances and replete as needed. • Monitor for signs and symptoms of infection. • Monitor complete blood counts frequently. • Monitor for infusion related AEs and treat as per guidelines.
Panitumumab (Vectibix)	Amgen	EGFR	Wild-type RAS metastatic colorectal caner	Acneiform dermatitis Pruritus Erythema Rash Skin exfoliation Paronychia Dry skin Skin fissures Diarrhea, Nausea/vomiting Fatigue Abdominal pain Overgrowth of eyelashes	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.

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Table 2: Contd...

Monoclonal antibodies (mAbs)	Company	Target	Indication	Common selected AEs	Management
					• 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.
Pertuzumab (Perjeta)	Genentech	HER-2	Metastatic breast cancer Neoadjuvant treatment of breast cancer	Nausea Diarrhea Fatigue Dry skin Alopecia Dermatitis Pruritus Neuropathy Cold symptoms	• Assess for signs and symptoms of infection. • Assess left ventricular ejection function and monitor for cardiac failure or dysfunction
Ramucirumab (Cyramza)	Amgen	VEGFR2	Non-small cell lung cancer Gastric cancer or GE Junction Colorectal cancer	Hypertension Diarrhea Headache, Hyponatremia Neutropenia Intestinal obstruction Blood clots Epistaxis	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.
Rituxin (Rituximab	Genentech	CD20	Low grade or follicular lymphoma Non-Hodgkin lymphoma Chronic lymphocytic leukemia	Infusion reactions Infections Myalgias Fatigue Nausea	• Assess for infusion related AEs • Premedicate with acetaminophen and antihistamine prior to each infusion. • Assess complete blood counts and renal function.
Trastuzumab (Herceptin)	Roche	HER-2	Adjuvant and Metastatic breast cancer Metastatic Gastric cancer	Fever Nausea/vomiting Infusion reactions Diarrhea Infections Increased cough Headache Fatigue Dyspnea Rash Neutropenia Anemia Myalgias Cardiomyopathy	• Assess for signs and symptoms of infection. • Assess left ventricular ejection function and monitor for cardiac failure or dysfunction.
Trastuzumab Emtansine (Kadcyla)	Genentech	HER-2	Metastatic breast cancer	Thrombocytopenia Elevated liver enzymes Hypokalemia Myalgia Arthralgia Anemia Neutropenia Fatigue Nausea Cardiomyopathy	• 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.

conduct surveillance.[36] The FDA has approved two CAR T-cell therapies: (1) axicabtagene ciloleucel (Yescarta: Kite, Santa Monica, CA) for adult patients with diffuse large B-cell lymphoma who have relapsed after two other kinds of treatment and (2) tisagenlecleucel (Kymriah: Novartis, Switzerland) for children and young adults with B-cell acute lymphoblastic leukemia.[37]

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 nephritic 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].[10,23,24]

Oncolytic viral therapy

Oncolytic viral therapy, which increases a patient's immune response to cancer without harming normal

Table 3: Checkpoint inhibitors

Checkpoint inhibitors[54-61,64,65]	Company	Target	Indication	Common selected irAEs	Management[58,60,61,64,65]
Atezolizumab (Tecentriq)	Roche/ Genentech Ltd	PD-L1	Metastatic nonsmall cell lung cancer Advanced urothelial cancer	Fatigue Diarrhea Fever Myalgias Hepatitis Pruritus Pneumonitis Dermatitis	Baseline Perform a baseline assessment of thyroid studies, complete blood counts, liver function, and metabolic panels, grade, and document them prior to starting each treatment, and at intervals of 6-12 weeks for the first 6 months after completing treatment Document any co-morbid conditions Evaluate baseline radiological examinations 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 Assess for infusion related AEs Interrupt or slow the rate of infusion for grade 1 or 2 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 Dermatologic irAEs 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 Gastrointestinal irAEs 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 Endocrine irAEs Thyroid 1. Check thyroid panel at baseline and prior to each treatment 2. Hormone replacement therapy for symptomatic hypothyroidism or TSH >10 3. Beta-blockers for symptomatic hyperthyroidism Diabetes mellitus Monitor blood glucose levels with each dose Lifestyle and diet modification as needed Endocrine referral if symptomatic or uncontrolled blood glucose levels Hepatic irAEs Evaluate liver function tests prior to starting every cycle of treatment 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 Treat with corticosteroids
Avelumab (Bavencio)	Merck	PD-L1	Metastatic Merkel cell cancer	Fatigue Myalgias Colitis Infusion reaction Dermatitis, Hypothyroidism Hyperthyroidism Hyperglycemia Nephritis Hepatitis	
Durvalumab (Imfinzi)	Astra Zeneca	PD-L1	Unresectable stage III non-small cell lung cancer Urothelial cancer	Fatigue Colitis Fever Myalgias	
Ipilimumab (Yervoy)	Bristol-Myers Squibb Co	CTLA-4	Melanoma Combined with Nivolumab for treatment of advanced renal cell cancer, and microsatellite instability high or mismatch repair deficient metastatic colorectal cancer	Fatigue Diarrhea Colitis Pruritus Myalgias Dermatitis Hepatitis	
Nivolumab (Opdivo)	Bristol-Myers Squibb Co	PD-1	Metastatic melanoma Metastatic non-small cell lung cancer Advanced renal cell cancer Metastatic urothelial cancer Classical Hodgkin lymphoma Recurrent/metastatic squamous cell cancer of the head and neck Hepatocellular cancer	Fatigue Myalgias Dermatitis Diarrhea Hypothyroidism Colitis Hepatitis, Pneumonitis	
Pembrolizumab (Keytruda)	Merck and Co Inc	PD-1	Advanced nonsmall cell lung cancer Classical Hodgkin lymphoma Advanced gastric cancer Advanced melanoma Microsatellite instability-High cancer Advanced cervical cancer Head and neck squamous cell cancer	Fatigue Dermatitis Arthralgias Cough Hyperglycemia Hepatitis Pruritus	

Contd...

Table 3: Contd...

Checkpoint inhibitors[54-61,64,65]	Company	Target	Indication	Common selected irAEs	Management[58,60,61,64,65]
			Advanced urothelial bladder cancer Primary mediastinal B-cell lymphoma		Grade 3- Treatment should be permanently discontinued Start corticosteroids If no response to steroids, mycophenolate mofetil should be started Consider hepatologist referral and liver biopsy Pulmonary irAEs Grade 1- Hold treatment; re-evaluate in 1-2 weeks, repeat chest imaging after 3-4 weeks as needed Grade 2- Assess for infection, monitor every 3-7 days, if no improvement in 48-72 hours, start methylprednisolone Grade 3-4- Discontinue treatment permanently, hospital admission, referral to infectious disease Musculoskeletal irAEs Mild- Continue treatment, NSAIDS Moderate- Consider holding treatment, prednisone, consider rheumatology referral if symptoms do not improve Severe- Consider discontinuation of treatment, methylprednisolone and infliximab, and rheumatology referral

irAEs: Immune-related adverse events, CTLA-4: Cytotoxic T-lymphocyte-associated protein 4, NSAIDS: Nonsteroidal anti-inflammatory drugs, PD-1: Programmed cell death-1, TSH: Thyroid-stimulating hormone

tissue, uses a modified virus that can force tumor cells to self-destruct and release antigens.[13] 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.[51] 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.[52] 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.[51,52] 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].[25]

Immune checkpoint inhibitors

Immune checkpoint inhibitors, which enhance the immune system's preexisting antitumor responses, target molecules that switch immune responses on and off.[8] 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.[53] 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 varies malignant cells.[53] 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.[54] The FDA has approved several checkpoint inhibitors that have shown clinical efficacy in the treatment of a number of cancers [Table 3].[54-57]

The AEs associated with checkpoint inhibitors are referred to as immune-related AEs (irAEs).[56] These irAEs are secondary to the infiltration of activated T-cells – which are also involved in autoimmunity – into normal tissue.[10] 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.[47,56,58-61] For example, in a retrospective study of 50 patients with nonsmall cell lung cancer, who were treated with an immune checkpoint inhibitor, the

Figure 1: Clinical steps for assessing and managing immune-related adverse events[58]

most frequent irAEs were fatigue (42%), rash (22%), nausea (20%), and fever (20%).[62] 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%).[63]

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.[58,60,64,65] 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 [Figure 1].[58]

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.[60] Furthermore, patients and caregivers should be educated in early recognition and management of irAEs to minimize serious or life-threatening complications.[66] 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).[67] 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.[57] 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.[57]

As checkpoint inhibitors are combined with other immunotherapy agents or other treatment modalities, the likelihood of more severe or newer AEs occurring increases.[66] 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.[68] 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.[69]

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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Conflicts of interest

There are no conflicts of interest.

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