



Cancer Immunotherapies: What the Perioperative Physician Needs to Know

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Abstract

Purpose of Review For patients with cancer, treatment may include combination therapy, including surgery and immunotherapy. Here, we review perioperative considerations for the patient prescribed immunotherapeutic agents.

Recent Findings The perioperative period is a poignant moment in the journey of a patient with cancer, potentially deemed most influential compared to other moments in the care continuum. Several immunotherapeutic medications have been employed near the time of surgery to potentially increase effectiveness. Of the various drug classes, including immune checkpoint inhibitors, cytokines, toll-like receptor agonists, and oncolytic viruses, among others, several notable immune-related adverse effects were noted. They range from minor effects to more serious ones, such as renal failure, myocarditis, and tumor growth.

Summary Surgery and immunotherapy are often employed in combination for primary treatment and prevention of cancer recurrence. Careful review and consideration of the pharmacokinetics, pharmacodynamics, and toxicities of immunotherapy benefit the perioperative physician and their patients.

Keywords Immunotherapy · Cancer · Perioperative

Introduction

The perioperative period is often stressful for the patient—involving a major surgery, extensive preparation, a hospital admission and stay, and recovery phase. For those patients with cancer, it often presents further challenges. The surgical stress and inflammatory response can be magnified by promotion of angiogenesis, tumor shedding and release into the circulation, proliferation of tumor growth factors, facilitation of distant organ metastatic colonization, and weakened immune surveillance [1]. Even if surgery is successful in

removing the primary tumor, there is often residual disease, either as dormant or active tumor cells and micrometastases. The myriad of immunological processes that can synergistically promote metastases in the immediate perioperative period emphasizes the importance of a favorable immune balance for long-term cancer survival [1].

Combination therapy—cancer surgery and immunotherapy—is not a straightforward treatment strategy. Patients may experience more pronounced side effects and limitations before any synergistic benefit [2]. Immunostimulation may pose unwanted dysregulations in wound healing, infections, and overall recovery [2]. In certain patient populations, and for particular cancer types, perhaps the benefits outweigh the risks.

The tumor microenvironment consists of numerous molecules that yield cellular apoptosis, DNA damage, and faulty cellular repair. Their interaction with innate and adaptive immune cells can help predict whether the immune system can mount a greater pro-tumorigenic or anti-tumorigenic response to cancer [3]. The immune system consists of deeply connected and interrelated cellular networks and signaling for both non-specific and acquired cellular defenses (Fig. 1) [4]. Targeting cells, ligands, signaling

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Overview of Innate and Adaptive Immunity

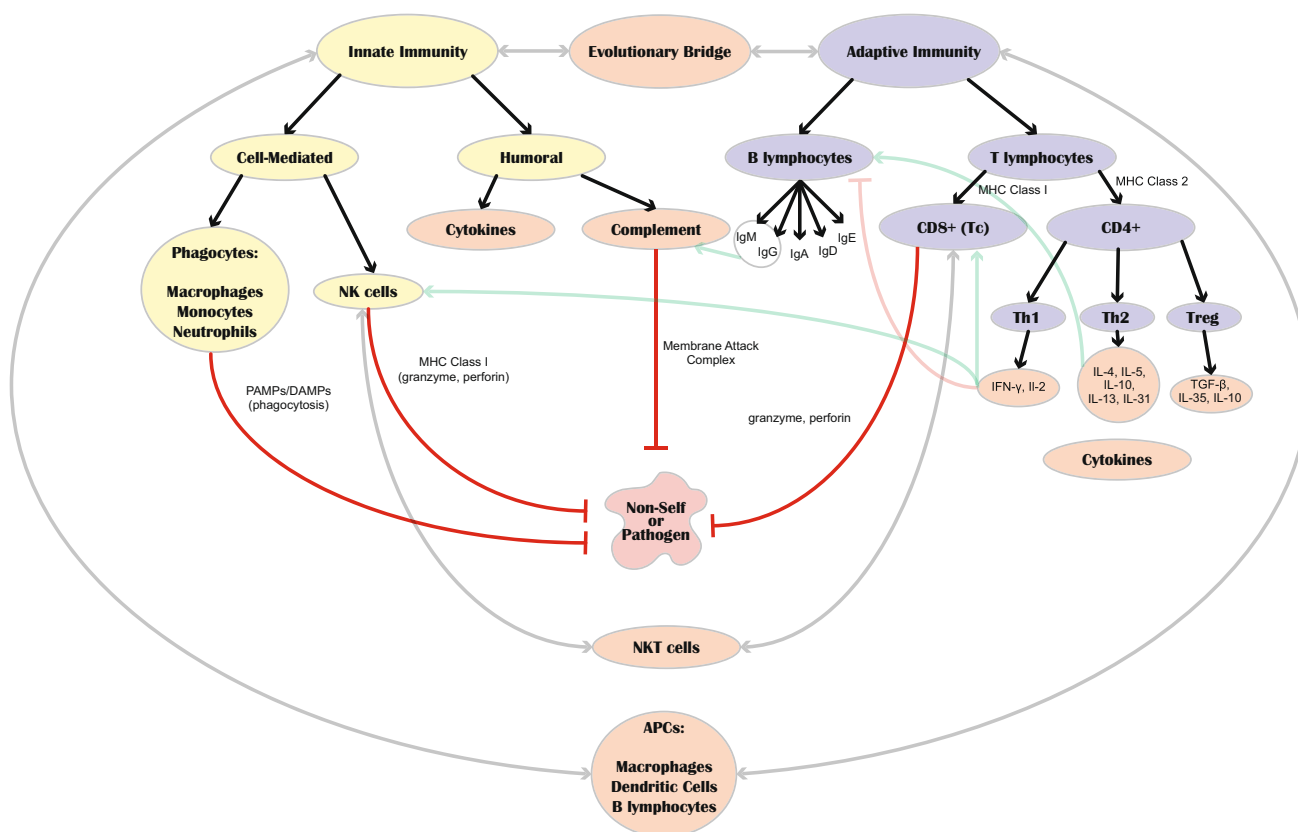


Fig. 1 Overview of innate and adaptive immune system. Solid gray arrow: evolutionary link; solid green arrow: activation; solid red arrow: inhibition. APC indicates antigen presenting cell; CD4+, cluster of differentiation 4 positive; CD8+, cluster of differentiation 8 positive; IFN- γ , interferon gamma; IgA, immunoglobulin A; IgD, immunoglobulin D; IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M; IL-2, interleukin 2; IL, interleukin;

MHC, major histocompatibility class; NK, natural killer; NKT, natural killer T cell; reg, regulatory T cell; Tc, cytotoxic T cell; TGF β , transforming growth factor beta; Th1, T helper type 1; Th2, T helper type 2. Reproduced with permission from: Ackerman RS, Luddy KA, Icard BE, Piñero Fernández J, Gatenby RA, Muncey AR. The Effects of Anesthetics and Perioperative Medications on Immune Function: A Narrative Review. *Anesth Analg*. 2021;133(3):676–689

molecules, and cytokines has become increasingly effective as cancer immunotherapeutics were applied to more and more patients [5].

In this review, we highlight the major medication classes in modern immunotherapy—immune checkpoint inhibitors, cytokines, toll-like receptor agonists, targeted antibodies, adoptive cell therapy, cancer vaccines, and oncolytic viruses, among others (Table 1). We explore the implications for the patient with cancer undergoing surgery and considerations for the perioperative physician and care team.

Immunomodulators

Various immunomodulators, such as immune checkpoint inhibitors (ICI), cytokines, and toll-like receptor agonists and adjuvants, have been increasingly prescribed for

anti-tumor and oncologic indications. In addition to the basic goals of studying efficacy and safety, the perioperative clinician should act to identify biomarkers predicting positive and negative responses and assess for increased or decreased efficacy with combination therapies [6]. Furthermore, complex perioperative decisions include appropriate patient selection, optimal duration and timing of adjuvant or neo-adjuvant therapy, anticipated and unexpected side effects and toxicities, scheduling of operative procedures, and methods of clinical response and re-staging, among many others [7].

Immune Checkpoint Inhibitors

Tumor cells utilize immune checkpoints such as programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) to evade T-cell recognition and immune response.

Table 1 Classification of Immunotherapy for Cancer with examples of specific agents

Immunomodulators	Targeted antibodies	Adoptive cell therapy	Cancer vaccines	Oncolytic viruses
Immune checkpoint inhibitors (ICIs) Ipilimumab, nivolumab, pembrolizumab	Unconjugated monoclonal antibodies Rituximab, pertuzumab, cetuximab, bevacizumab	Chimeric antigen receptor (CAR) T cell therapy Axicabtagene ciloleucel, lisocabtagene maraleucel	Therapeutic BCG, sipuleucel-T	Talimogene laherparepvec (T-VEC)
Cytokines GM-CSF, interferon alfa, aldesleukin	Antibody–drug conjugates (ADCs) Belantamab mafodotin-blmf, brentuximab vedotin	Tumor-infiltrating lymphocyte (TIL) therapy	Personalized neoantigen	
Toll-like Receptor (TLR) Agonists & Adjuvants Imiquimod, poly ICLC	Bispecific antibodies, including Bispecific T-cell engagers (BiTEs) Amivantamab, blinatumomab	Engineered T cell receptor (TCR) therapy	Preventive HPV and HBV vaccines	
Other Pexidartinib		Natural killer (NK) cell therapy		

Granulocyte–macrophage colony-stimulating factor (*GM-CSF*), polyriboinosinic-polyribocytidylic acid (*poly-ICLC*), human papillomavirus (*HPV*), hepatitis B virus (*HBV*), Bacillus Calmette-Guerin (*BCG*)

Immune checkpoint inhibitors (ICI), while often efficacious for anti-tumor response, yield a myriad of toxicities and autoimmune reactions that limit their generalizability and application [8•]. Ipilimumab, an antibody against CTLA-4, is approved for use against metastatic melanoma, renal cell carcinoma, and colorectal cancer. The anti-PD-1 nivolumab and pembrolizumab have indications for late-stage lung cancer, Hodgkin's lymphoma, hepatocellular carcinoma, metastatic urothelial carcinoma, and gastric and esophageal tumors, among others [9]. Furthermore, the anti-PD-L1 atezolizumab, durvalumab, and avelumab can be prescribed for metastatic triple-negative breast cancer, lung cancer, Merkel cell carcinoma, and metastatic urothelial carcinoma [9].

In general, ICI are believed to be safe in the perioperative period and for many different surgery types, with a low likelihood of grade III or IV Clavien-Dindo complications observed. They likely do not need to be stopped before surgery [10]. Interestingly, a positive association has been described with the development of immune-related adverse events after the use of ICI therapy and progression-free survival (PFS), overall survival (OS), and objective response rate (ORR). However, for higher toxicities, this association was observed for ORR, but not OS [11]. Numerous biomarkers have been and are being studied as predictors for toxicity, including those associated with the tumor microenvironment, circulating blood, targeted organs, and host. Examples include cellular counts (e.g., eosinophils), HLA genotypes, circulating tumor cells, gut microbiota diversity, drug dosage, tumor burden, and serum proteins [12].

Neurologic toxicities are rare in patients receiving ICI, a prevalence of 1–5%. However, when present, the consequences can be severe, with significant morbidity and mortality observed [13]. The most common neurologic adverse effects include myasthenia gravis-like symptoms,

peripheral neuropathies such as Guillain–Barre syndrome, and meningo-encephalitis. Treatment includes ICI discontinuation, high-dose steroids, and supportive care [13].

ICI-related acute kidney injury (AKI) is hypothesized to be from acute tubular nephritis via reactivation of effector T-cells by nephrotoxins, increased PD-L1 expression by tubular cells, or loss of tolerance against renal self-antigens. In certain populations, such as the renal transplant recipient treated with ICI, rejection is an increased concern [14].

ICI-associated cardiotoxicity is relatively rare compared to other immune-related adverse effects. However, life-threatening ventricular tachyarrhythmias and complete atrioventricular block have been reported [15]. Review of electrocardiogram (ECG), biomarkers, and cardiac symptoms should guide medical decision making. Abnormal ECG, elevated biomarkers, and moderate to severe symptoms may yield permanent discontinuation of ICI, extended-duration high-dose corticosteroids, and other immunosuppressive or risk-controlling therapies [15].

General symptoms of ICI toxicity included fevers, chills, and lethargy [16]. Dermatologic toxicities were usually maculopapular in nature [16]. Gastrointestinal distress was most commonly diarrhea and colitis, with or without ulceration. Hepatotoxicity manifested as elevated transaminases. Endocrinopathies were more pronounced, featuring hypophysitis, thyroiditis, and most dangerously, adrenal insufficiency [16]. Pulmonary toxicity ranged as mild as pneumonitis and pneumonia to severe hypoxia and ARDS [17].

ICI-induced vasculitis is rare, but potentially life-threatening. Most seen are those affective larger vessels, such as giant cell arteritis, thought to be related to PD-1 mechanisms. Paraneoplastic vasculitis should also be surveilled in patients on these unique medications [18].

In terms of perioperative considerations for the anesthesiologist and surgeon, preoperative assessment must include a review of cardiopulmonary status and inquiry into possible treatment-related toxicities, especially after ICI initiation or titration. Laboratory studies can include blood counts, chemistry panels, endocrine hormone levels, baseline troponin or B-natriuretic peptide, and HgbA1c [19, 20•]. Furthermore, as deemed necessary, further cardiac and pulmonary studies can be obtained including ECG, transthoracic echocardiogram, pulmonary function tests, chest plain films, and CT scans, among other tests [20•].

Cytokines

Immunostimulatory cytokines, such as interleukin-2 (IL-2), granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor alpha (TNF- α), and interferon-alpha (IFN- α), promote natural killer (NK) cell activity and yield benefits in reduce cancer metastases and recurrence [21]. NK cells have anti-tumor properties via its direct cytotoxicity, cytokine secretion, apoptosis induction via death receptor ligand expression, and contribution to antibody-dependent cell-mediated cytotoxicity [21]. Thus, interleukins and interferons have been proposed and applied to various cancer types as non-specific immunotherapeutic agents [3].

High-dose IL-2 (HDIL-2) has been approved for treatment of melanoma and metastatic renal cell cancer. IL-2 is a T-cell growth factor, promoting antigen-activated CD8 T-cells, CD4 T-cells, and NK cells; it also acts as a stimulator of the immunosuppressive T-regulatory (Treg) cells [22, 23]. HDIL-2 has a short serum half-life and has several notable toxicities. Elevated endothelial cell-induced vasodilation and angiopoietin-2 and nitric oxide synthase predispose to vascular leak syndrome [22]. Other severe systemic effects include pulmonary edema, hypotension, myocarditis, thrombocytopenia, and renal insufficiency [24]. Furthermore, HDIL-2 preferentially induced the immunosuppressive Treg cells. The above sequelae limit its clinical application [22].

Interleukin-15 (IL-15) has been more recently explored due to its stimulation of activated T-cell proliferation, cytotoxic T lymphocyte production, and (indirectly) immunoglobulin synthesis by B-cells without activation of Treg cells [22]. Toxicities include fever, thrombocytopenia, and hypotension [25]. Compared to IL-2 therapies, extensive capillary leak syndrome has not been observed [22]. Early evidence shows promise in treatment of leukemia, metastatic melanoma, and lung cancers.

Interleukin-15 receptor subunit alpha (IL-15R α) has been investigated against IL-15 due to its more potent activation of NK cells [25]. Unfortunately, subcutaneous administration was associated with inflammation up to 30 cm, limiting the dose of IL-15 that could be prescribed [22].

Other cytokine therapies have been studied, or are being studied, and have yet to be applied broadly or yield promising results. IFN- γ never demonstrated oncologic efficacy and has been used mostly for osteopetrosis and chronic granulomatous disease [22]. IFN- α was approved for treatment of melanoma, AIDS-related Kaposi's sarcoma, and hairy cell leukemia, among other cancers, but has been relegated to lower line therapy due to novel agents proving more efficacious [22]. Patients treated with IFN often experienced fever, fatigue, depression, diarrhea, nausea, hyper- or hypothyroidism, and anorexia; hepatotoxicity was observed in up to 10% of patients [16]. IL-7, IL-21, and combination cytokine therapy need further study prior to its prescription and application for cancer treatment [22, 24].

Toll-Like Receptor Agonists and Adjuvants

Toll-like receptors (TLR) represent a promising target for novel immunotherapeutic agents. A variety of selected receptors have been applied for treatment of bladder, breast, lung, skin, gastric, and hepatocellular cancers [26]. Each receptor interacts with different ligands (lipoproteins, DNA, RNA, peptides, etc.), arises from diverse sources (bacteria, viruses, fungi, unknown), and provides unique functions (dendritic cell expression, PAMP recognition, downstream cellular signaling) [27]. TLR are the best-defined pattern recognition receptor (PRR) and trigger an innate immune cascade of cytokine induction, antigen presentation, chemokine release, and co-stimulation of related molecules. In natural killer (NK) cells, they induce NK cytotoxicity and production of cytokines [28].

For patients with cancer undergoing solid organ transplantation, such as those with hepatocellular carcinoma, TLR have been implicated in acute allograft rejection [27]. Ischemia-reperfusion injury can be mediated by TLR signaling and release pro-inflammatory cytokines and chemokines; dendritic cell maturation may yield effector T-cells resistant to host suppressive methods, initiated graft rejection [27].

Bacillus Calmette-Guerin (BCG) therapy has been described as a treatment for bladder cancers, stimulating TLR2/4 and TLR9 [29]. This live and attenuated *Mycobacterium bovis* has previously been used for a tuberculosis vaccine. Specific anti-tumor activity is related to secretion of interferon-gamma and interleukin-2 [30]. Local side effects are most common, including cystitis, dysuria, and hematuria. Systemic side effects have also been described, including fever, sepsis, and death [30]. Treatment benefits for other cancers have not been demonstrated for BCG.

Imiquimod targets TLR7 and has FDA approval for the treatment of basal cell carcinoma. Anti-tumor mechanisms are hypothesized from recruitment of tumor-infiltrating dendritic cells and macrophages, and ultimately infiltration of helper T-cells [29]. Imiquimod is applied topically

and thus has few systemic side effects, local skin reactions being the most common adverse effect [29].

Resiquimod, a TLR7/8 agonist, has anti-viral properties and is under investigation for use in malignant skin tumors. Local skin reactions are the most common toxicity reported, with no patients reportedly experiencing grade 2 or worse adverse events [29]. Resiquimod is being examined in comparison to imiquimod, as well as a topical vaccine adjuvant [29].

Monophosphoryl lipid A (MPLA), a lipopolysaccharide derivative, has been employed as a vaccine adjuvant, such as the hepatitis B and HPV vaccines, to further active in the innate immune response, potentially against lower immunogenic antigens, such as those associated with tumors [29]. MPLA is well tolerated with no increase in adverse effects compared to placebo, but has yet to be approved for cancer therapy [29].

The derivative of polyriboinosinic-polyribocytidylic acid (poly-ICLC) stimulates cellular signaling via TLR3, resulting in direct tumor cell apoptosis and has been described one of the strongest tumor vaccine adjuvants [29]. Positive survival benefits have been described in adult and pediatric gliomas, with neutropenia as the most common adverse effect when prescribed with adjuvant chemotherapy and radiation. As a pure vaccine adjuvant, fewer and lower grade adverse effects were observed [29].

Other Immunomodulators

Pexidartinib was approved in 2019 by the FDA for treatment of symptomatic tenosynovial giant cell tumors (TGCT) in patients with severe limitations or morbidity and deemed unamenable to surgery [31]. This novel medication is a tyrosine kinase inhibitor and acts potently and selectively against the colony-stimulating factor 1 (CSF1) receptor, as well as KIT proto-oncogene receptor tyrosine kinase and FMS-like tyrosine kinase 3 [32]. TGCT aberrantly express CSF1, attracting inflammatory cells that compose the bulk of the tumor. Early studies, including the phase 3 randomized ENLIVEN trial, have been positive, with overall response rates ranging from 39 to 53% compared to placebo [33]. The most notable adverse complication is cholestatic and mixed hepatotoxicity, identified in roughly 10% of patients with transaminases (AST, ALT) potentially greater than three times the upper limit of normal and alkaline phosphatase twice the upper limit [33]. A boxed warning of hepatotoxicity was applied, and caution should be made when administering in context of other hepatically cleared or toxic medications. In the USA, access to patients is limited via a risk evaluation and mitigation strategy program [32].

Targeted Antibodies

Targeted antibodies are a form of cancer immunotherapy that directly target tumor cells. These antibodies are designed to specifically bind a target on the tumor cell surface or tumor microenvironment leading to tumor cell death via a variety of mechanisms, including activation of the host immune response. Some targeted antibodies bind targets on tumor cells and immune cells. Targeted antibodies can be categorized into three types: unconjugated monoclonal antibodies (mABs), antibody–drug conjugates (ADCs), and bispecific antibodies (bsABs).

Unconjugated Monoclonal Antibodies

Unconjugated mABs (also known as naked mABs) are the most common type of targeted antibody. As of August 2021, there were 19 targeted, unconjugated mABs available in the USA with Food and Drug Administration (FDA) approval for the treatment of cancer, including various solid tumor and hematological malignancies [34, 35]. The variable or fragment antigen-binding (Fab) region of these mABs target tumor-associated antigens and disrupt tumor cell signaling activity required for growth and survival. Unconjugated mABs also induce immune cell-mediated tumor cell killing, via the constant or fragment crystallizable (Fc) region of the antibody [36, 37].

The first mAB indicated for treatment of cancer, rituximab, was approved by the FDA in 1997 for non-Hodgkin B-cell lymphoma [38]. It binds the cluster of differentiate (CD) 20 antigen which is overexpressed on tumor cells relative to mature human B-cells (and not expressed on immature human B-cells) leading to tumor cell death via antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), and complement dependent cytotoxicity (CDC). Other targeted, naked mABs were approved in the USA shortly thereafter, including trastuzumab in 1998 for treatment of breast cancer, which targets human epidermal growth factor receptor 2 (HER2) and bevacizumab in 2004 for colorectal cancer, which targets vascular endothelial growth factor (VEGF) [39, 40]. Trastuzumab binds HER2, a tyrosine kinase receptor that is overexpressed on tumor cells in certain types of breast (among other) cancers, inhibiting its hetero-dimerization, thereby blocking activation of growth factors necessary for tumor survival [41]. Rather than ligand or receptor blocking on the tumor cell surface, bevacizumab binds VEGF, an angiogenic cytokine overproduced in the tumor microenvironment, which prevents it from binding its receptor, and suppresses angiogenesis required for tumor growth [42]. Other naked mABs that

target CD20 (obinutuzumab and ofatumumab), HER2 (pertuzumab and margituximab), and VEGF (ramucirumab) subsequently received FDA approval, for chronic lymphocytic leukemia (CLL), breast cancer, and gastric cancer, respectively [34, 35]. Notwithstanding, rituximab, trastuzumab, and bevacizumab remained among the top 10 best-selling mABs in 2018 [43].

In addition to CD20, HER2, and VEGF, other targets of FDA-approved unconjugated mABs include epidermal growth factor receptor (EGFR), disialoganglioside GD2, CD19, CD38, CD52, signaling lymphocytic activation molecule family 7 (SLAMF7), and C–C motif chemokine receptor 4 (CCR4). EGFR-targeted, unconjugated mABs are used in treatment of solid tumors and include cetuximab, approved in 2004 for colorectal cancer (CRC) and 2006 for head and neck squamous cell carcinoma; panitumumab in 2006 for CRC; and necitumumab in 2015 for non-small cell lung cancer. GD2-targeted, unconjugated mABs are also used in treatment of solid cancers, with dinutuximab and naxitamab-gqgk approved for neuroblastoma in 2015 and 2020, respectively. CD52-, CD38-, and CD19-targeted, unconjugated mABs are used in treatment of hematologic malignancies, and include alemtuzumab for B-cell CLL, daratumumab and isatuximab for multiple myeloma, and tafasitamab-cxix for diffuse large B-cell lymphoma, respectively. Other naked mABs used in treatment of blood cancers include the SLAMF7-targeted mAB, elotuzumab, FDA approved for multiple myeloma, and CCR4-targeted mAB, mogamulizumab, for cutaneous T-cell lymphoma [34, 35].

Antibody Drug Conjugates

Building on the efficacy of targeted, unconjugated mABs, ADCs were developed to take advantage of the antigen-specificity of mABs as a mechanism for delivering a cytotoxic substance (i.e., anti-mitotic drug, drug that causes DNA damage, exotoxin, or radionuclide) directly to tumor cells. The efficacy of the ADC relies not only on the mAB target and the cytotoxic payload, but also on the linker between them [44]. In 2000, the FDA approved the first ADC, gemtuzumab ozogamicin, for treatment of acute myeloid leukemia. Gemtuzumab ozogamicin targets CD33, expressed on surface of leukemic blasts but not hematopoietic stem cells, and is conjugated to calicheamicin, a DNA-damaging drug; it was withdrawn from the US market in 2010 and reapproved in 2017 with altered dosing schedule yielding reduced adverse effects and improved efficacy [45]. The second ADC to enter the US market was the radioisotope-linked mAB ibritumomab tiuxetan, approved in 2002 for non-Hodgkin's lymphoma, and remains the only FDA-approved targeted radioimmunotherapy (RIT) [46].

Almost two decades later, many more ADCs have been approved for hematological malignancies including

brentuximab vedotin (in 2011 for Hodgkin's lymphoma and anaplastic large-cell lymphoma), inotuzumab ozogamicin (in 2017 for acute lymphoblastic leukemia), moxetumomab pasudotox (in 2018 for hairy cell leukemia), polatuzumab vedotin (in 2019 for B-cell lymphoma), belantamab mafodotin-blmf (in 2020 for multiple myeloma), and loncastuximab tesirine-lpyl (in 2021 for large B-cell lymphoma) [34, 35]. These ADCs target CD30, CD22, CD79B, B-cell maturation antigen (BMCA), and CD19. Their cytotoxic payloads include the anti-mitotic tubulin inhibitors monomethyl auristatin E and F (MMAE and MMAF, respectively), the DNA-damaging agents calicheamicin, pyrrolobenzodiazepine dimer (PBD), and the exotoxin *Pseudomonas* exotoxin A (PE38).

ADCs have also been approved for treatment of solid malignancies, beginning with ado-trastuzumab emtansine (or T-DM1, in 2013 for breast cancer), followed by enfortumab vedotin (in 2019 for bladder cancer), fam-trastuzumab deruxtecan-nxki (or T-DXd, in 2019 for breast cancer), and sacituzumab govitecan-hziy (in 2020 for triple negative breast cancer). These ADCs target HER2 and trophoblast cell surface antigen 2 (Trop-2), which are overexpressed in breast cancers, and Nectin-4 which is abundantly expressed in urothelial cancer. Their cytotoxic payloads include the antimitotic tubulin inhibitors emtansine (DM1) and MMAE, and the DNA-damaging topoisomerase I inhibitors deruxtecan (DxD) and irinotecan metabolite (SN-38) [34, 35].

Bispecific Antibodies

The latest advance in the development of targeted mABs is the bsABs, which can target two different antigens. Targeting two different tumor-associated antigens can help overcome the challenge of clinical resistance seen with cancer treatments [47]. A subcategory of bsABs, the bispecific T-cell engagers (BiTEs), target both tumor cells and immune cells; bridging tumor cells with T-cells leads to T-cell activation and tumor cell lysis. There are only 2 bsABs currently on the US market; however, Labrijn et al. reported more than 85 bsABs were being developed for clinical use as of March 2019 [48]. The first bsAB to gain regulatory approval in the US was blinatumomab, for relapsed/refractory acute lymphoblastic leukemia (ALL), in 2014. It is a BiTE that binds both CD19 (consistently found on ALL blasts) and CD3 (on cytotoxic T-cells) facilitating malignant cell lysis [49]. The second bsAB for treatment of cancer, amivantamab, was approved in 2021 for non-small cell lung cancer (NSCLC). Amivantamab targets EGFR and MET, which are overexpressed on the NSCLC tumor cell surface and implicated in TKI drug resistance; amivantamab impedes tumor cell survival via EGFR and MET ligand blocking, receptor degradation, and host-immune response stimulation via ADCC [47].

Perioperative Considerations with Targeted Antibodies

Due to the efficacy of targeted antibodies, despite varied response rates across cancer types and within subsets of a specific cancer, their clinical study and use continue to expand. The perioperative physician will encounter with increasing frequency patients who are being treated or have been treated with targeted antibodies for cancer. They are used in both neoadjuvant and adjuvant settings, and as monotherapy as well as in combination with other cancer treatments such as chemotherapy and radiation. General understanding of their mechanism of action as described above, as well as knowledge of treatment-related adverse effects and their perioperative implications as follows, is vital to the perioperative management of these patients.

Compared with traditional chemotherapy, targeted antibody immunotherapy is generally associated with less toxicity due to its specificity in targeting cancer cells over normal tissue [50]. The spectrum of adverse effects (AEs) of targeted antibodies is broad, ranging from infusion reactions to cardiovascular, pulmonary, neurologic, renal, and hepatic toxicities [50, 51•]. The development of AEs is related to the antigen(s) targeted by the antibody, cancer type, administration of other cancer treatments, and patient's comorbidities. Perioperative considerations vary depending upon the type and severity of AEs.

Immediate infusion-related reactions (IRRs) commonly occur with administration of targeted mABs, and etiology includes anaphylaxis, anaphylactoid reactions, and cytokine release syndrome (CRS) [51•]. Higher dose, infusion rate, and tumor burden are risk factors for IRRs. Serious IRRs occur with the anti-CD agents rituximab, ibritumomab tiuxetan, alemtuzumab, brentuximab, and blinatumomab; the anti-HER2s, trastuzumab and pertuzumab; the anti-EGFRs, cetuximab and panitumumab; and the anti-VEGF bevacizumab [52]. The anti-GD2s, dinutuximab and naxitamab-gqgk, also have boxed warnings for serious IRRs [53, 54]. Kounis syndrome, a hypersensitivity-mediated acute coronary syndrome, has been reported with rituximab infusion, and implicated in cases of ACS with cetuximab and alemtuzumab [55]. Analgesia with fentanyl is recommended over morphine and acetaminophen intravenous in these cases, due to less mast cell degranulation with the former [56]. Polymorphic ventricular tachycardia has also been reported with rituximab infusion [57]. CRS manifestations include fever, hypotension, and hypoxia, and management includes anti-pyretics, corticosteroids, and supportive care for organ failure [58]. Rare, delayed IRRs, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and serum-sickness like reactions can also occur [58]. The preoperative history and physical (H&P) should note the date of last targeted mAB infusion, incidence and severity of IRRs, and

treatment received for IRRs and consider sequelae of IRRs and their treatment in the perioperative period (i.e., organ failure, hyperglycemia from corticosteroid administration).

Cardiovascular (CV) adverse effects have been reported with HER2-, VEGF-, and EGFR-targeted antibodies. All 5 anti-HER2 antibodies on the US market are associated with cardiotoxicity, and the greatest CV risk is with trastuzumab [59]. Risk factors include advanced age, comorbid cardiac disease, and treatment with anthracyclines. Reduced ejection fraction (EF)/ heart failure risk is not dose-dependent and may be reversible. Lisinopril and carvedilol were cardioprotective in patients treated with both anthracyclines and trastuzumab [60]. Both VEGF-targeting antibodies, bevacizumab and ramucirumab, have CV toxicities including hemorrhage, gastrointestinal perforation, impaired wound healing, hypertension, and thromboembolic events; bevacizumab also exhibits dose-dependent increased risk of cardiac and cerebral ischemia and heart failure [61•]. Due to impaired wound healing, these agents should be held at least 28 days before and after surgery. Additionally, bevacizumab thrombotic risk was related to cancer type (increased with CRC but not breast cancer) which the authors postulated may be due to shared comorbid risk factors for CV disease and CRC or to differences in combined treatment regimens. Of the approved anti-EGFR antibodies, panitumumab, cetuximab, and necitumumab have increased risk of venous thromboembolism [61•, 62]. The latter two also carry boxed warnings for cardiopulmonary arrest/sudden death and are associated with hypomagnesemia (electrolytes should be monitored) but not QTc prolongation [63, 64]. The anti-CD22, moxetumomab pasudotox, has a boxed warning for capillary leak syndrome (CLS), a rare disorder associated with high mortality, that manifests with edema, hypotension, hypoalbuminemia, and hemoconcentration; treatment is supportive [65]. In addition to performing a preoperative H&P with emphasis on elucidating signs and symptoms of cardiovascular pathology, consider additional preoperative testing in patients treated with HER2-, VEGF-, and EGFR-targeted antibodies, to include electrocardiogram (ECG), echocardiogram, complete metabolic panel (CMP), including magnesium, potassium, calcium, and albumin, and complete blood count (CBC). Detection of abnormalities should guide intraoperative management (i.e., invasive monitoring, goal-directed fluid management) and postoperative care (i.e., telemetry monitoring) and maintain increased vigilance for cardiovascular complications during the perioperative period.

Pulmonary toxicity has also been documented with targeted antibodies, including anti-CD20 rituximab, anti-EGFRs cetuximab and amivantamab-vwmjw, and most notably, anti-HER2 agents. In a recent review, Hacksaw et al. reported the incidence of interstitial lung disease (ILD)/ pneumonitis associated with anti-HER2 agents,

including trastuzumab, T-DM1, and T-DXd; ILD incidence was highest with trastuzumab in combination with everolimus (7.3–21.4%) and ILD-related deaths highest with T-DXd (1.7–2.2%) [66]. Treatment involves dose interruption, reduction, and/or discontinuation and corticosteroids; consensus is lacking for ILD monitoring in this setting. Perioperative pulmonary complications may be increased in patients treated with these agents. Acute respiratory distress syndrome after mastectomy was reported in a patient who received neoadjuvant therapy that included trastuzumab [67]. The perioperative physician should review the past medical history (PMH) for ILD or treatment with targeted antibodies associated with pulmonary toxicity, elicit signs and symptoms of such, and consider chest imaging and pulmonary function testing, to help guide intraoperative management (i.e., lung protective ventilation) and postoperative monitoring (i.e., continuous pulse oximetry) and care.

Neurotoxicity of varying incidence and severity has been documented with targeted antibody therapy. More than 50% of patients treated with blinatumomab, the CD19 targeted BiTE, experience neurologic AEs, including encephalopathy, seizures, and cerebellar changes (abnormal coordination and balance) [50, 68•]. Risk of cerebrovascular accident is increased with bevacizumab (due to increased thromboembolic events) and alemtuzumab. Progressive multifocal leukoencephalopathy (PML), a rare neurologic infection, has been reported with anti-CD agents, including rituximab, obinutuzumab, ofatumumab, alemtuzumab, and brentuximab vedotin. Posterior reversible encephalopathy syndrome (PRES), which manifests with headaches, vision changes, and seizures, occurred in patients treated with trastuzumab (HER2), bevacizumab (VEGF), cetuximab (EGFR), naxitamab-gqgk (GD2), and rituximab (CD20) [51•]. Cetuximab is also associated with aseptic meningitis and hypomagnesemia leading to cramps, fatigue, and somnolence. Anti-GD2 agents may cause severe neuropathic pain that may require opioid analgesics during and after infusion [54]. Perioperative neurologic complications may be increased in patients treated with these agents. Postoperative paraplegia has been reported after uneventful spinal for urologic surgery in a patient treated with maintenance obinutuzumab 3 weeks prior to surgery; history of neurologic signs and symptoms was not evident until postop [69]. Perioperative care in patients treated with targeted ABs associated with neurotoxicity should include a preop H&P with focus on history of neurologic symptoms, thorough neurologic exam, and review of neurologic imaging, testing, and consultations. Electrolyte abnormalities (i.e., hypomagnesemia, often with concomitant hypocalcemia) should be corrected preop. Perioperative analgesic regimen should be tailored for patients receiving chronic opioid analgesia with careful consideration of potential for increased risk with regional or neuraxial analgesia in the setting of pre-existing neurologic

injury; continuation of anti-epileptics, effects of preoperative corticosteroids (i.e., adrenal insufficiency, hyperglycemia), and close blood pressure monitoring are additional considerations. Anesthetic management should aim to facilitate prompt recovery to preoperative mental status and facilitate timely postoperative neurologic assessment.

Renal AEs can also occur with targeted mABs. Anti-CD agents, alemtuzumab and moxetumomab pasudotox, have boxed warnings for autoimmune reactions (including anti-glomerular basement membrane disease) and hemolytic uremic syndrome, respectively [70, 71]. Tumor lysis syndrome and CRS can cause acute kidney injury (AKI), as seen with anti-CD20 agents, rituximab and obinutuzumab [72]. Nephrotic syndrome, interstitial nephritis, and thrombotic microangiopathy (TMA) have been reported with the anti-VEGF mABs, bevacizumab, and ramucirumab [73]. Preoperative renal function should be assessed (i.e., CMP) and history of renal dysfunction elicited. Additional considerations during the perioperative period include avoidance of nephrotoxic drugs; renal dose adjustment, as indicated; and special attention to blood pressure and fluid management.

Hepatotoxicity has been noted with several targeted antibodies, including CD- and HER2-targeted agents. On meta-analysis, the relative risk of high-grade transaminitis in patients with breast cancer treated with T-DM1 (anti-HER2) was more than double that of controls [74]. Exposure to anti-CD agents, gemtuzumab ozagamicin, and inotuzumab ozagamicin, increases the risk of hepatic veno-occlusive disease (VOD) after stem cell transplant for treatment of leukemia, and is associated with high mortality in severe cases [75]. Patients treated with anti-CD20 agents (rituximab, obinutuzumab, and ofatumumab) for non-Hodgkin lymphoma are at very high risk of hepatitis B virus (HBV) reactivation that, if unrecognized, can lead to life-threatening hepatic dysfunction; monitoring and anti-viral prophylaxis for those at high risk are recommended [76]. The perioperative physician should assess for history, signs, and symptoms of hepatic dysfunction and assess hepatic function with labs, preop. Consider delays in elective surgery for resolution of serious hepatic AEs.

Hematologic AEs with targeted antibodies, such as cytopenia and special considerations in blood transfusion, impact the perioperative period. Sacituzumab govitecan (anti-TROP2) and the RIT ibrutinomab tiuxetan carry boxed warnings for neutropenia and severe prolonged cytopenias, respectively [46, 77]. Assess CBC, and consider correction of cytopenias preoperatively. Anticipate need for additional time to obtain blood products in patients with multiple myeloma treated with anti-CD38 agents (daratumumab and isatuximab) as these agents cross-react with red blood cells resulting in false-positive indirect anti-globulin tests; a neutralizing agent against the CD38 mAB must be added during the crossmatch [78]. Consider preoperative

type and crossmatch, notify blood bank of patients being treated with these agents, and maintain heightened vigilance for transfusion reaction.

Adoptive Cell Therapy

Adoptive cell therapy represents a variety of treatments in which immune effector cells are genetically engineered to recognize and eliminate cancer cells. This discussion will focus on the only commercially available adoptive therapy currently: chimeric antigen receptor (CAR) T-cell therapy, which has shown great promise for refractory B-cell lineage malignancies with response rates of 50–90% [79•]. Other early-stage experimental adoptive cell therapies include T-cell receptor-engineered T-cell (TCR-T) therapy, natural killer (NK) cell therapy, and tumor-infiltrating lymphocyte therapy, which to date have poorly defined toxicity profiles [80–82]. The genetic manipulation of immune effector cells to bind to and destroy malignant cells comes with significant side effects related to the actual engineered cells themselves and the immune response they create and the necessity of lymphodepleting agents [79•, 83•].

CAR T-cell therapy is a form of immunotherapy in which T-cells are engineered to target and kill cancer cells. There are two primary types of native T-cells, CD4+ and CD8+. CD4+ T-cells are subdivided into type 1 helper T (Th1) cells, which produce IFN- γ and IL-2 and enhance cell-mediated immunity and NK cell cytotoxicity, type 2 helper T (Th2) cells which produce interleukins that serve to increase humoral immunity and control of antibody production, and regulatory T-cells, which reduce inflammation through production of TGF- β , IL-35, and IL-10. CD4+ T-cells require co-stimulation with MHC class II on antigen-presenting cells (APCs) to properly target an antigen and save it to immunological memory. CD8+ T-cells are cytotoxic T-cells which are MHC class I restricted and serve to directly kill abnormal cells (cell-mediated immunity) [84, 85].

CAR T-cells include both CD4+ and CD8+ T-cell types but differ from native T-cells in that they are engineered to function independently of MHC co-stimulation. Rather, the chimeric antigen receptor is designed with a built-in co-stimulation moiety to allow T-cell proliferation in the absence of MHC. Additionally, the chimeric antigen receptor contains a moiety to specifically target an antigen expressed by the type of cancer cells being treated, but not expressed by normal cells within the body [86, 87].

CAR T-cells are created by taking autologous or allogeneic blood via leukapheresis and harvesting native T-cells. The native T-cells are then transfected with the genes encoding the chimeric antigen receptor either with a viral (adenovirus, lentivirus, or retrovirus) or non-viral (transposon)

vector. Cellular division and proliferation of the newly created CAR T-cells is induced in the laboratory under exposure to stimulating cytokines, which are then cryopreserved. The patient is conditioned with a lymphodepleting agent such as fludarabine or cyclophosphamide 3–5 days prior to injection of CAR T-cells; this prevents competition with native T-cell populations [79•, 87].

There are currently five FDA-approved CAR T-cell therapies on the market: axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel, brexucabtagene autoleucel, and idecabtagene vicleucel [88]. Axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel, and brexucabtagene autoleucel are all designed to target the CD19 antigen found on B-cell lineage malignancies and are used to treat refractory B-cell lymphomas and mantle cell lymphoma [79•, 83•, 88–92]. Idecabtagene vicleucel targets B-cell maturation antigen (BCMA) which is uniquely overexpressed in myeloma cells; it is approved for the treatment of refractory multiple myeloma [87, 93].

It is worth noting that FDA approval for CAR T-cell therapies is restricted to refractory malignancies that have failed previous treatment modalities [88, 90–93]. This is due to potentially life-threatening side effects, which preclude widespread use.

The most common toxicity associated with CAR T-cell therapies is cytokine release syndrome (CRS); a constellation of inflammatory symptoms initiated by CAR T-cell activation, cytokine release, and activation of other immune cells. CRS is seen in 70–95% of patients undergoing CAR T-cell therapy with median onset of 2 days (though onset can be delayed up to 14 days) postinjection. The exact mechanism has not yet been elucidated but is likely related to activation of the vascular endothelial system. Clinically, patients present with fever and depending on the severity, hypoxia, and hypotension. Severe cases may also lead to coagulopathy, hypoalbuminemia, and multiorgan failure [79•, 83•].

The hallmark of CRS is fever, which has a 100% sensitivity and 84% specificity for CRS within 36 h of CAR T-cell infusion. The American Society for Transplantation and Cellular Therapy has created the following consensus grading criteria: grade 1, temperature ≥ 38 °C, no hypotension, no hypoxia; grade 2, temperature ≥ 38 °C, hypotension not requiring vasopressors, hypoxia requiring low-flow nasal cannula; grade 3, temperature ≥ 38 °C with hypotension requiring a vasopressor and/or hypoxia requiring high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask; and grade 4, temperature ≥ 38 °C, hypotension requiring multiple vasopressors (excluding vasopressin), and hypoxia requiring positive pressure (CPAP, BiPAP, or mechanical ventilation) [94].

Tocilizumab, a monoclonal antibody against the IL-6 receptor, is an FDA-approved treatment for severe or life-threatening CRS and has been shown to produce rapid

resolution of symptoms without negatively impacting CAR T-cell proliferation or persistence, necessary for therapeutic effect. Glucocorticoids can be used to treat CRS but are considered 2nd line and only for life-threatening cases due to evidence that the immunosuppression may decrease efficacy of the CAR T-cell therapy itself. The optimal dose and timing to initiate glucocorticoids have not been well established. Siltuximab, a monoclonal antibody that binds directly to IL-6, has been used off label to treat CRS refractory to tocilizumab and steroids, with good result [83•].

The second most common CAR T-cell-associated toxicity is neurotoxicity, which usually occurs concurrently with CRS. The most typical manifestation is encephalopathy with or without expressive aphasia. Severe cases can result in seizures, cerebral edema, brain herniation, and death, and the mechanisms are not understood. The median time to presentation is 5 days, and median length of symptoms is 10 days. EEG typically shows diffuse, generalized slowing and often imaging shows no evidence of disease. ICP is often elevated with opening pressures ≥ 20 mmHg. In a study of CD19-targeted CAR T-cells for B-ALL, 40% of 133 total patients experienced a grade 1 or higher neurological event, 5% developed grade 4 neurotoxicity, and 3% died secondary to neurotoxicity in the first 28 days. Ninety one percent of patients had CRS preceding neurotoxicity. Higher disease burden prior to CAR T-cell treatment and high peak CAR T-cell activity are predictive of neurotoxicity [83•].

Grade 1 or 2 neurotoxicity is managed supportively with close monitoring, EEG, CNS imaging, and aspiration precautions. Tocilizumab, which does not cross the blood brain barrier, should not be used in cases of neurotoxicity independent of CRS, and glucocorticoids are the preferred agent for grade 2 or higher neurotoxicity without CRS. For grade 1 or higher neurotoxicity in the presence of grade 2 or higher CRS, tocilizumab is the preferred treatment. Seizure prophylaxis with levetiracetam is also warranted in cases of neurotoxicity and for those patients at high risk to developed neurotoxicity. Intraoperatively, patients with known severe neurotoxicity should be presumed to have elevated ICP and treated accordingly. Benzodiazepines and/or propofol may be used to treat seizure activity [79•, 83•].

Patients who have recently undergone CAR T-cell therapy should not be scheduled for elective surgery. If emergency surgery is required, the anesthesiologist and surgeon should have a basic understanding of CRS and neurotoxicity and be prepared to support the patient with vasopressors, mechanical ventilation, anti-seizure medications, and ICP precautions if needed. BMP, renal function, and coagulation factors should be assessed, and patients must be closely monitored for development of fever. Close communication with the oncology team is important, and glucocorticoids should never be administered without their approval. Treatment with tocilizumab, siltuximab, and/or glucocorticoids

may be warranted, and this should also be discussed with the oncology team [79•]. Antibiotic prophylaxis is important as these patients are lymphodepleted and high infection risk [83•]. The choice of antibiotic may be discussed with the oncology team.

Advancement of CAR T-cell constructs and newer immunotherapies such as NK cell therapy, tumor-infiltrating lymphocytes, and T-cell receptor-engineered T-cell (TCR-T) therapy hold promise for avoiding the toxicities associated with CAR T-cell therapy but will likely come with their own novel set of side effects, which are to date not well defined [80–82].

Cancer Vaccines

Human Papillomavirus Vaccines

There are 2 types of human papillomavirus (HPV) vaccines that are FDA approved currently. The first-generation, bivalent, and quadrivalent Cervarix and Gardasil are effective against HPV strains 16 and 18. In addition, Gardasil protects against HPV 6 and 11 [95]. The second generation includes the nine valent Gardasil 9, effective against HPV strains 6, 11, 16, 18, 31, 33, 45, 52, and 58.

HPV vaccines protect against cervical, vulvar, vaginal, anal, penile, and oropharyngeal cancers and genital warts. All 3 vaccines are synthetically manufactured virus-like particles (VLPs) of the oncogenic protein subunit L1 of the various HPV types [95]. Although the exact mechanism of action is unknown, it is believed that the vaccine works by activating the humoral response system. HPV L1VLP vaccination induces high titers of genotype-restricted neutralizing antibodies and is highly effective at preventing HPV infection and thereby the neoplastic diseases they cause [96]. It is also reported that antibody titers for 9vHPV are 10–100-fold higher than that of natural infection [97].

Clinical trials have shown that all the vaccines are highly effective at preventing persistent type specific HPV infection [98, 99]. Population-based data also demonstrates that effective implementation of HPV vaccine may substantially reduce the burden of HPV related disease and medical procedures [100]. Long-term effectiveness was also observed through up to 8 years postvaccination for the 9vHPV vaccine [101].

According to the CDC report based on Vaccine Adverse Event Reporting System (VAERS) from June 2006 to March 2013, approximately 56 million doses of HPV vaccines were distributed in the USA, resulting in 21,194 adverse events following immunizations (AEFIs). Ninety-two percent were non-serious including syncope, dizziness, nausea, headache, fever, and urticaria. The most frequently reported serious (7.4%) AEFI's included headache, nausea, vomiting, fatigue,

dizziness, syncope, and generalized weakness [102]. There have been some isolated case reports and a few case series of postural orthostatic tachycardia syndrome (POTS), CRPS, and fibromyalgia after HPV vaccination [103].

In addition, HPV vaccination has also been associated with a collection of symptoms, indicating nervous system dysfunction [104]. There are some studies relating these heterogeneous postvaccination symptoms to immune dysfunction activated by adjuvants or ASIA (autoimmune/auto-inflammatory syndrome induced by adjuvants) [105]. Perioperative evaluation should include a detailed history and physical examination and measurement of blood pressure and heart rate in while supine and 1, 3, and 5 min in upright position. Valsalva maneuver can test several components of the baroreflex arc [106]. More detailed autonomic function testing like tilt-table testing and heart rate variability monitoring may be needed for select patients [107].

Identification of patients with a chronic pain disorder preoperatively is necessary to facilitate adequate postop recovery and rehabilitation. This includes obtaining a detailed history and physical examination, medication history, formulating a robust multimodal analgesic regimen, use of regional anesthetic techniques when feasible, and a conversation about realistic expectations of postoperative pain control.

Hepatitis B Virus Vaccines

Hepatitis B virus (HBV) vaccines include the conventional Recombivax HB and Engerix-B, CpG-adjuvanted Heplisav-B and several combination vaccines such as Twinrix (hepatitis B & A) and Pediarix (DTap & IPV). They are all non-infectious recombinant DNA vaccines containing hepatitis B surface antigen (HBsAg). Vaccination produces antibodies against the surface antigen of all genotypes (A-H) of the virus and gives broad immunity, thereby preventing hepatocellular carcinoma related to HBV.

The novel immunostimulatory adjuvant CpG (cytosine phosphoguanine oligodeoxynucleotide) in Heplisav-B is proposed to activate toll-like receptor 9 (TLR9) on plasmacytoid dendritic cells which, when combined with HbsAg enhances HbsAg—specific memory cells and antibody production [108].

The safety and efficacy of HepB vaccines have been well established. Over 1000 million doses of Hep B vaccines have been administered with an excellent safety record. Research shows hepatitis B vaccine to be safe for all age groups [109]. AS04C-adjuvanted hepatitis B vaccine showed a 100% response rate in HIV patients and an excellent safety profile [110].

The most frequently reported side effects were injection site pain, redness, fatigue, and vomiting [111]. Individual case reports of rare adverse effects like multiple sclerosis and

optic neuritis have been described although a causal association has not been established [112]. There was no significant difference in the side effect profile between the HepB-CpG and Engerix-B vaccines [113]. However, an increased risk of MI and new-onset autoimmune events including PMR, UC, and autoimmune thyroiditis were observed in clinical trials [114]. Perioperative considerations should include assessment of cardiovascular and neurological function and labs to assess thyroid function.

Prostate Cancer Vaccine

Sipuleucel-T PROVENGE® (Dendreon pharmaceuticals) is an autologous dendritic cell-based vaccine approved by the FDA in 2010 for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant (hormone-refractory) prostate cancer. Autologous dendritic cell precursors are incubated with PAP2024—a recombinant fusion protein composed of the prostate-specific antigen (PSA) known as prostatic acid phosphatase (PAP) fused to granulocyte-macrophage colony-stimulating factor (GM-CSF) and incorporated into Dendreon's proprietary antigen delivery cassette [115].

The most common adverse effects reported are chills, fatigue, fever, back pain, nausea, joint ache, and headache [116]. No studies of drug interaction have been performed with Sipuleucel-T. Acute infusion reactions are possible. Thromboembolic events include deep venous thrombosis, pulmonary embolism, and cerebrovascular and cardiovascular events like hemorrhagic and ischemic strokes, TIA, and MI [117]. Most patients with metastatic prostate cancer have multiple risk factors for these events at baseline. Perioperative evaluation should include detailed cardiac and neurologic history and work up.

Oncolytic Viruses

Talimogene laherparepvec (T-VEC) under the trademark name of IMLYGIC™ (AMGEN Inc., Thousand Oaks, CA) is currently the only FDA-approved oncolytic virus, designed for use in unresectable stage IIIB to IV non-visceral melanoma which recurs after initial surgery [99, 118]. It is a live, attenuated, genetically modified herpes simplex type 1 virus (HSV). T-VEC's design involves taking wild-type HSV and removing two genes: the herpes neurovirulence factor gene, ICP34.5 and ICP47. By removing ICP34.5, the virus becomes less pathogenic and replicates more selectively in tumor cells. Deleting the ICP47 gene reduces virus-mediated suppression of antigen presentation [118]. Furthermore, the virus is modified by inserting the gene that encodes human granulocyte macrophage colony-stimulation factor (GM-CSF) which, when expressed, activates antigen-presenting

cells to induce a tumor-specific T-cell response and enhance dendritic cell function. The virus replicates within tumor cells, causes tumor lysis, and releases tumor-derived antigens to further trigger an anti-tumor immune response [99, 118–120].

In a phase III study of 436 patients with advanced stage, unresectable melanoma randomized to receive T-VEC versus GM-CSF only, T-VEC treatment showed a higher durable response and, although not statistically significant, a trend towards better overall survival (hazard ratio [HR] 0.79; 95% CI 0.62–1.00). Median overall survival with T-VEC treatment was 23.3 months (95% CI, 19.5 to 29.6 months). T-VEC was well tolerated, with the most common side effects being low-grade fever, chills, myalgias, and reactions at the site of injection [99, 118, 120, 121].

T-VEC is injected directly into cutaneous or subcutaneous lesions or into lymph nodes. Dosing is based on size of lesion. The initial dose is followed by a subsequent dose 3 weeks later and then other doses, if necessary, at 2-week intervals [99]. Patients wear a bandage over injection sites until up a week after each treatment [119]. The usual treatment length of time is at least 6 months with continued or resumed injection for new lesions that develop. T-VEC is not approved for use in immunocompromised or pregnant patients [99, 118–120].

Perioperative clinical considerations start with preoperative assessment of organ function. Patients with pre-existing auto-immune disease are more prone to developing glomerulonephritis, vasculitis, pneumonitis, worsening psoriasis, and vitiligo during T-VEC treatment [99]. Therefore, labs to assess kidney function and close cardiovascular and pulmonary assessment may be warranted.

Other considerations include a risk of accidental exposure to healthcare workers with subsequent herpetic infection. The greatest risk of a disseminated herpetic infection is in an immunocompromised person, and therefore, these individuals should exhibit particular caution when caring for a patient undergoing oncolytic viral therapy. If a patient has been recently injected with T-VEC, it is recommended that healthcare providers and close contacts avoid direct contact with lesions, dressings, or bodily fluids of the treated patient. In a recent study of patients who received treatment, during cycles 1–4, IMLYGIC™ DNA was found in the blood in 98.3% patients, urine of 31.7% of patients, treated lesions of 100% of patients, exterior dressings of 80% of patients, and oral mucosa and anogenital region of 8% of patients. Percentage of patients with viral DNA at various sites decreased over time with repeat testing. Among all samples, only swabs from the surface of injected lesions tested positive for infectivity [119]. Another study found that actual infectious virus was present at the injection site in 15% of patients within the first week after the initial injection, whereas the outer layer of dressing was positive for IMLYGIC™ DNA

in 70% patients at some point during the study, but no actual virus was found in that location [99]. The highest amount of virus or DNA was present in the first two cycles of treatment with very little by the end of treatment [99]. Patients undergoing this treatment may also present with active herpetic lesions including oral lesions. Therefore, when caring for these patients perioperatively, universal precautions, with particular attention to gloves and eye protection, should be practiced. Despite the theoretical risk however, no actual transmission to healthcare workers or caregivers has been reported at this point [99, 119].

Regarding the use of medications in the perioperative setting that may interfere with treatment, there is a paucity of data on drug interactions. The only drugs that should definitively be avoided are anti-herpetic agents as they can interfere with viral efficacy [99]. Treatment injections can result in cellulitis, tissue necrosis, open wounds, and even systemic bacterial infection. Care should be taken when establishing intravenous access, placing monitors, and positioning patients that any bandages from therapy stay on and no lines placed near sites of cellulitis or infection [99].

Genetically engineered oncolytic viruses are currently being evaluated in clinical trials for a wide range of solid tumors including breast, glioma, head and neck, pancreatic, and hepatocellular carcinoma. Therefore, it will likely become more common to treat patients perioperatively who are undergoing these therapies underscoring the importance of maintaining familiarity with these emerging treatments [122].

Conclusion

The clinical use of immunotherapy for treatment of cancer continues to expand, and there are many new agents in the pipeline. Perioperative medicine physicians will increasingly encounter patients treated with cancer immunotherapies. Knowledge regarding these agents' mechanisms of action, adverse effects, and their perioperative implications facilitates optimal perioperative care.

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