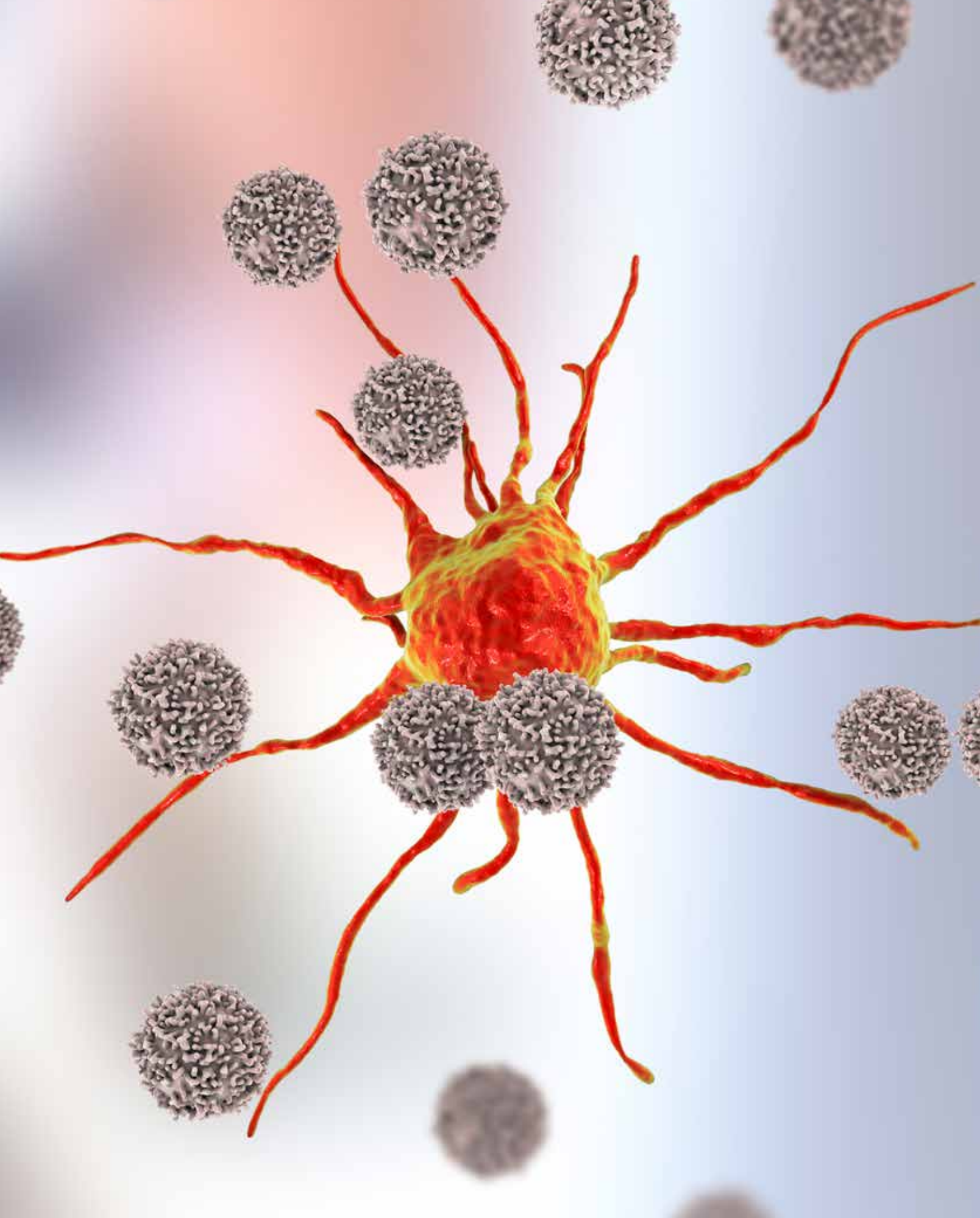

Use of Surgery and Immunotherapy to Treat Cancer

Kassandra Bahr, CST, CFA, DBA

Surgical removal of tumors and intravenous immunotherapy to treat specific cancers (bladder, kidney, prostate, melanoma) have been shown effective in patients through immune checkpoint therapy, adoptive cellular therapy, cytokine therapy, and more recent oncolytic viral therapy.

The idea of cancer immunotherapy dates back to the Greek physician, Galen, who connected the inflammatory response to cancer. Later, two German physicians, Busch and Fehleisen, observed tumor regression after an erysipelas infection (skin bacterial infection similar to cellulitis). In 1891, the most noteworthy advances resulted from William Coley, known as the Father of Immunotherapy, who experimented with the immune system in bone cancer treatment. Coley expanded on the work of Busch and Fehleisen; he injected various mixtures of live *Streptococcus pyogenes* (bacteria in erysipelas skin infection) into patients' tumors. Coley noted significant tumor remission in sarcoma, lymphoma, and testicular cancers.[2] In 1945, there was renewed interest in the immune system and cancer research with the discovery of interferon and the work of Ruth and John Grahams on the first cancer vaccine. Then in 1967, Jacques Miller noted the existence of T cells and their role in immunity.[3] The knowledge and process of immunology

LEARNING OBJECTIVES

- Describe the history of immunotherapy
- Discuss the monoclonal antibody process
- List the types of adoptive cellular therapy
- Detail the combination strategies of surgeries and immunotherapy
- Review the side effects of immunotherapy

continue today with the use of bone marrow transplant as a treatment for hematological cancers. Another researcher at this time, Lloyd J. Old, realized that cancer cells are unique and different from normal cells and that this difference can be recognized by the human immune system. Professor Old theorized that immunotherapy would be used with chemotherapy, radiation, and surgery to treat cancer patients. In 1981, the first vaccine based on a single cell surface antigen became available – a hepatitis B vaccine – propelling the research to current developments.[4] Finally, as a result of research, which began in the 1950s, scientists determined the body's lymphocytes might act as soldiers to identify and eliminate cancer cells. Experiments with the mechanisms of tumor-specific antigens continued, and in the mid-twentieth century, Schreiber, Dunn, and Old proved that T cells were capable of providing anti-tumor immune response and surveillance.[5] Later, discoveries included the process of immunoediting (lab growth of cells) and the identification of a molecular target in cloning the melanoma antigen.

INTRODUCTION – THE BODY'S IMMUNE SYSTEM

The immune system is made up of white blood cells, organs and tissues of the lymph system – all work together to help the body fight disease and infection. Within the bloodstream, antibodies are blood proteins produced by plasma cells as a response to counteract an antigen (the unique molecule of the pathogen or invader cell). Antibodies or immunoglobulins combine with substances the body sees as foreign (bacteria, viruses). The concept of immunoglobulin in the body is to attack the cell's antigens and mark the cancer cell to be destroyed by immune system cells. Antibodies work in several ways: they signal the immune system and trigger an attack, or they interfere with the cancer cell signal, attempting to grow, divide, and spread.[6] White blood cells (known as T cells) help fight disease, and when the body senses an antigen, it releases T cells as self-defense. The antibody/immunoglobulin also marks a microbe or infected cell to be attacked by the immune system. In some cases, the antibody process may produce macrophages to destroy foreign bacteria or the virus. Simply stated, the immune system is designed to defend the body from disease and infection.

Cancer is a complex disease that can outsmart and evade the human immune system.[7] Cancer cells grow and spread because they hide from the body's immune system. Unfortunately, the immune system often does not recognize the cancer invader, and it grows out of control. The hallmark of malignancy is this immune evasion, and this is the reason cancer proliferates.[8] Once cancer cells begin to divide and spread in the body, the inflammatory response dampens the T cell immune response, preventing autoimmunity. Cancer cells in the tumor hijack T cell production to avoid being attacked.

Immunotherapy or infusion immune checkpoint inhibitor (ICI), help the body's immune system with a mark or target on the cancer cells. This is considered targeted therapy, and it makes it easier for the immune process to find and destroy invader cells.

Immune Checkpoint Therapy & Monoclonal Antibodies

Part of immunotherapy includes the development of therapeutic antibodies (known as monoclonal antibodies), which are created in the lab. These antibodies are designed to attack specific markers on cancer cells.[9] Part of the monoclonal antibody process is to mark cancer cells, which helps the immune system identify and destroy them. In addition, monoclonal antibodies may stop cancer cells from dividing/growing, or the monoclonal might carry toxins to other cancer cells. This targeted therapy process of monoclonal antibodies occurs when immune system proteins are created in the lab and then injected into the patient. The overall lab-created process of monoclonal antibodies are meant to interfere with the cancer proliferation by promoting T cell activation; this is also known as Infusion Immune Checkpoint Inhibitors (ICIs), and it has replaced chemotherapy in some cancer treatment.

Immunotherapy or infusion immune checkpoint inhibitor (ICI), help the body's immune system with a mark or target on the cancer cells. This is considered targeted therapy, and it makes it easier for the immune process to find and destroy invader cells. The immune system has a dual regulatory system of Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein (PD 1 or PD-L1 created in the lab) in the lymph tissue and tumor environment.[10] The CTLA-4 and PD1/PD-L1 pathways are what help the immune system control cancer growth; the pathways are considered immune checkpoints. Unfortunately, cancer may use these pathways to evade the

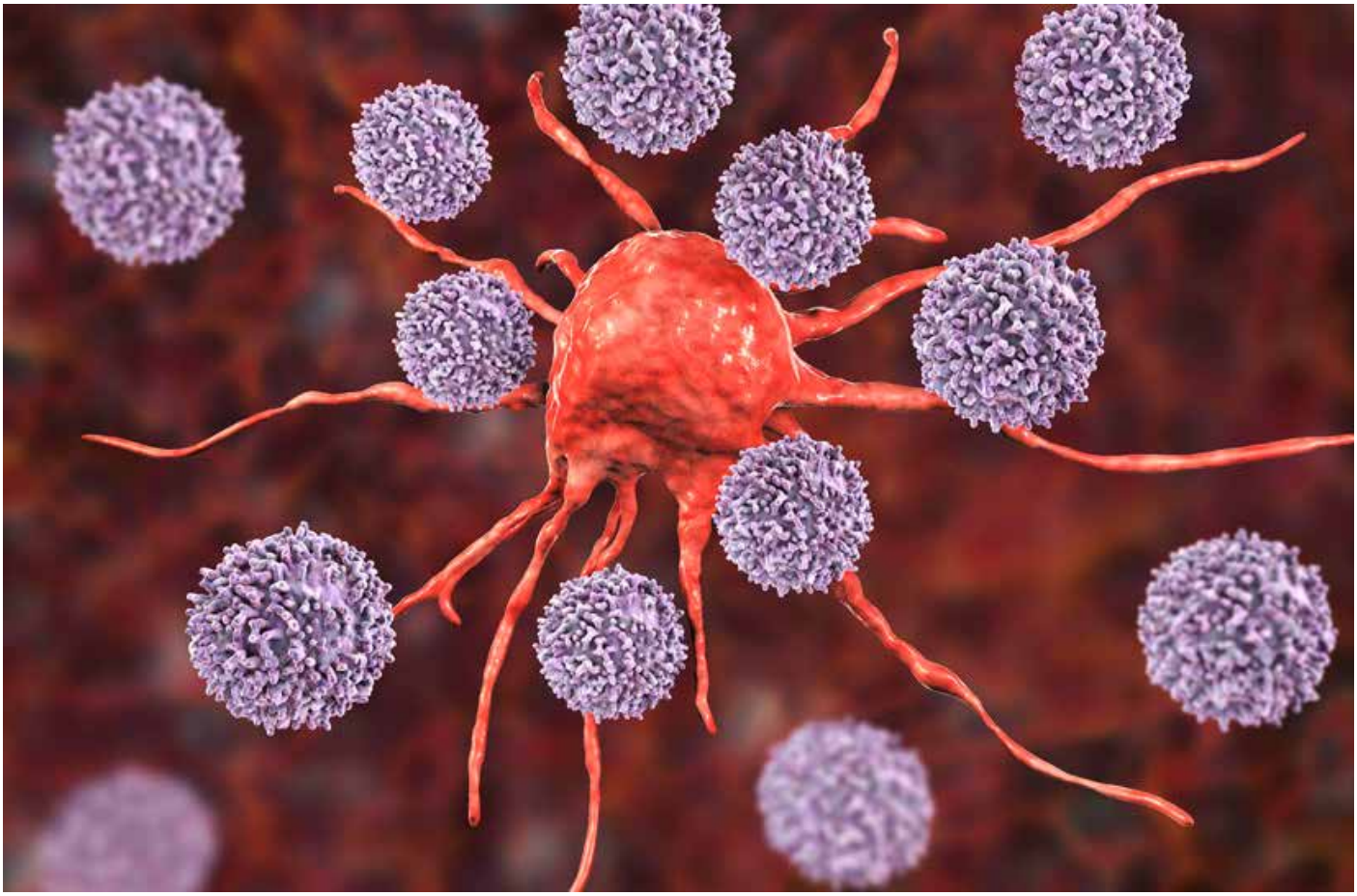

Figure 1[11] Harnessing T-cell responses against tumors is effective because these cells are highly specific, can be directed precisely to the cancer site, and have a memory, making them long-lasting.

immune system. The checkpoint inhibitors discussed previously are meant to block cancer's pathways with specific antibodies (ICIs). Immunotherapy, which is lab-created, may be delivered by intravenous method, or for specific tumors such as the bladder, melanoma, or kidney cancer, it may be surgically placed directly into the solid tumor. Helping the immune system find and identify the cancer is the first step in helping the body slow or stop cell growth.

ADOPTIVE CELL THERAPY (ACT)

The process of adoptive cell therapy works to increase the number and effectiveness of immune cells (T cells) in the body. Increasing and empowering T cells provides a stronger response against cancer. There are several types of adoptive cellular therapy: tumor-infiltrating lymphocyte (TIL), endogenous T cell (ETC) therapy, and chimeric antigen receptor (CAR) T cell therapy. Tumor-infiltrating lymphocyte and endogenous T cell therapy both involve a surgical procedure where T cells are removed from the cancerous tumor or from the patient's blood. In TIL therapy, patient T cells are extracted from a portion of the surgically removed cancerous tumor. In these cases, the patient's T cells are too few to fight cancer, and once they are removed and grown in the lab, their strength and number are more effective and productive when given back to the patient. Similarly, in ETC therapy, T cells are drawn from the patient's blood. The physician then selects the cells most able to recognize antigens in the cancer cells. These T cells need to be increased in number to find the cancer cells. The T cells that are determined to be most effective against the cancer are grown in a laboratory setting.[12] After cell growth in the laboratory (which lasts 3 to 8 weeks), the T cells are injected back to the patient's bloodstream. Generally, during the time cell growth is occurring in the laboratory setting, the patient will receive chemotherapy, which helps reduce the other types of immune cells in the

body. The idea is that chemotherapy helps clear the path for the lab-grown T cells to do their job in attacking the cancer.[13] Lastly, in Chimeric antigen receptor (CAR) therapy, T cells are removed from the patient's bloodstream. The patient undergoes a leukapheresis procedure where two intravenous lines are used: the line in one arm removes the whole blood from the body, and the line in the other arm has plasma, red blood cells, and platelets being returned to the patient.[14] The blood removed from the patient will have T cells separated from other white blood cells, and in the laboratory setting, the technician will add chimeric antigen receptors (CAR) to those T cells. Again, the laboratory growth and process require several weeks to create enough T cells needed to fight the cancer. The genetically engineered T cells are then injected back into the patient's bloodstream.

CYTOKINE THERAPY

Cytokine therapy involves immunotherapy designed to give assistance and help to the body's overall immune system, rather than targeting the tumor. Because the immune system is designed to fight invaders, making it more active and stronger can prove more effective in stopping cancer growth. Cytokines are proteins produced naturally and secreted by immune system cells.[15] Cytokines have an important role in sending signals to and between immune cells in the body. Cytokine therapy uses two specific proteins to trigger the immune response: interferons and interleukins. Both proteins are made in modified forms within the laboratory. Interferons work within the immune system to slow cancer cell growth, and the laboratory-created versions are known as interferon alpha (Roferon-A), Intron A, and Alferon.[16] Interferon cytokine treatment has been used to effectively fight leukemia, lymphoma, kidney, and melanoma. Interleukins are proteins, which help the body's immune system destroy cancer cells, and the laboratory-created versions are Interleukin-2 (IL-2) or aldesleukin (Proleukin). Interleukin cytokine treatment has been used to treat metastatic melanoma and advanced kidney cancer. Another form of immunotherapy in this category is Bacillus Calmette-Guerin (BCG), where a weakened strain of tuberculosis bacteria is injected directly into the bladder with a catheter.[17] The body recognizes the tuberculosis bacteria in the cells, and it sends macrophages to fight the invader. The effect of the BCG in the bladder causes an immune response against the cancer tumor.

ONCOLYTIC VIRAL THERAPY

A recently utilized form of cancer therapy that is generally classified as both immuno- and biological-therapy is oncolytic viral therapy. For tumors such as melanoma that are not treatable with surgery, the physician injects a genetically modified virus directly into the cancerous tumor.[18] Once the virus enters the cancer cells, it begins to make copies of itself which causes the cells to burst and die. Antigens are released at the cell's death, triggering the patient's immune system to target and attack the cancer cells with those same antigens. The laboratory created a genetically modified virus that does not enter healthy cells. A series of virus injections are generally required to eliminate the melanoma in oncolytic viral therapy.

The goal of immunotherapy is to coordinate surgery with the most appropriate immunological treatment to extend or eliminate the return of the patient's cancer.

SURGICAL PROCEDURES IN COMBINATION WITH IMMUNOTHERAPY

Surgery is a widely accepted standard of care for the removal of cancerous tumors. Cancerous tumors (lung, colorectal, liver, and breast) accounted for 8.8 million deaths in 2016.[19] Surgical removal is the primary treatment for these cancers. Unfortunately, the majority of these patients experience recurrent cancer within 5 years. The goal of immunotherapy is to coordinate surgery with the most appropriate immunological treatment to extend or eliminate the return of the patient's cancer. Clinical trials have shown that surgical tumor debulking may induce an inflammatory and metabolic event in patients, resulting in altered cytokine levels.[20] In response to the cancer surgery-induced immune reaction, research has been completed to discover ways to reverse metastatic disease postoperatively. Studies show the perioperative period is the most common time for cancer cells to metastasize.[21] In the past, patients recovering from cancer tumor removal

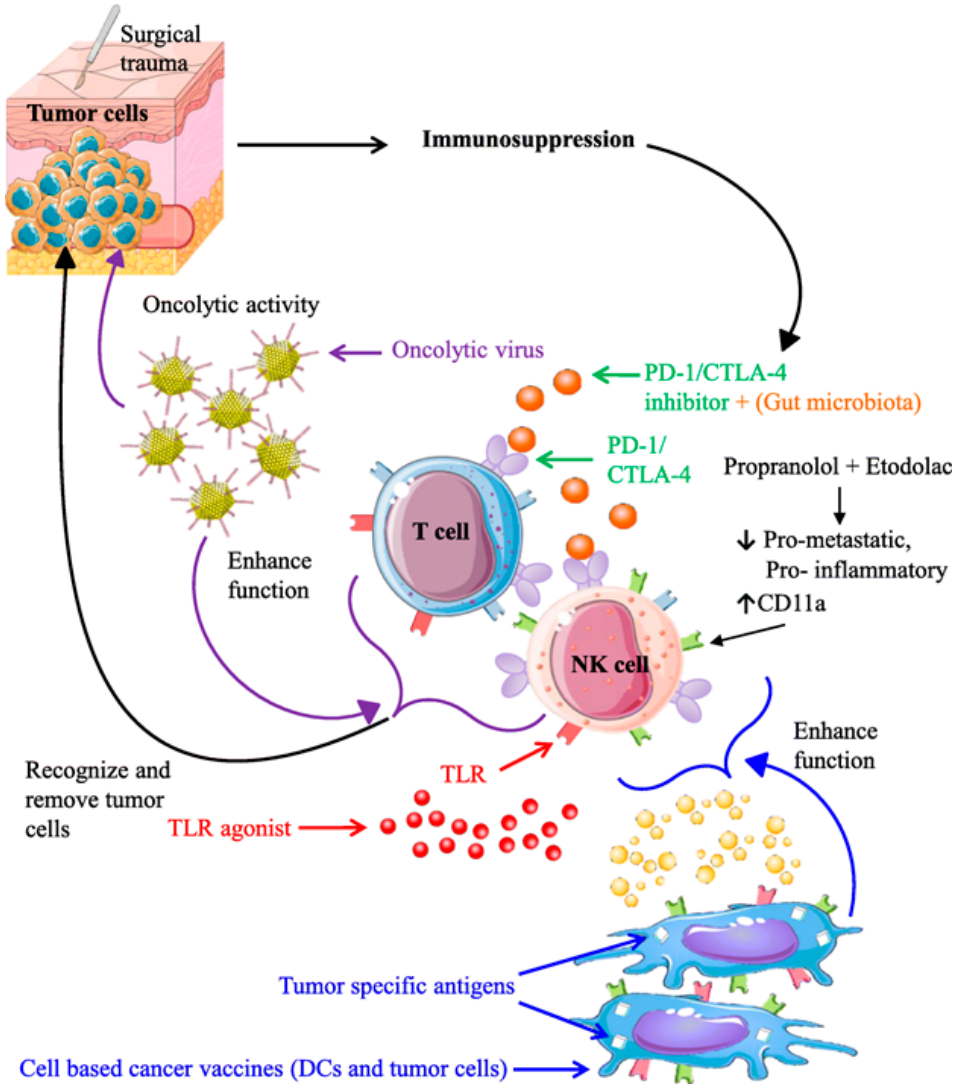

Figure 2[22] Combination strategies of surgery and immunotherapy

surgery did not undergo chemotherapy because of the detrimental effects on wound healing and the immune system. However, this perioperative window also presents an opportunity for physicians to boost the immune system and reduce or eliminate cancer recurrence. The most successful immunotherapy in these cases has been the previously discussed cytokine IL-2, used to stimulate the growth of lymphocytes.

Additional immunotherapy successful in perioperative treatment includes checkpoint inhibitors which have been shown to reduce postoperative T cell dysfunction.

TYPES OF CANCER TREATED WITH IMMUNOTHERAPY

Chemotherapy and Radiation with Immunotherapy

Common treatment methods for cancer combined with immunotherapy methods previously discussed generally include chemotherapy and/or radiation. The rationale of the multi-faceted treatment is based on the complexity of the cancer cell. The cancer tumor microenvironment (TME) includes fibroblasts, blood vessels and infiltrating immune cells.[23] Unfortunately, most of the pharmaceuticals used in chemotherapy to treat cancer have an immunosuppressive effect on the body. Also, there are some

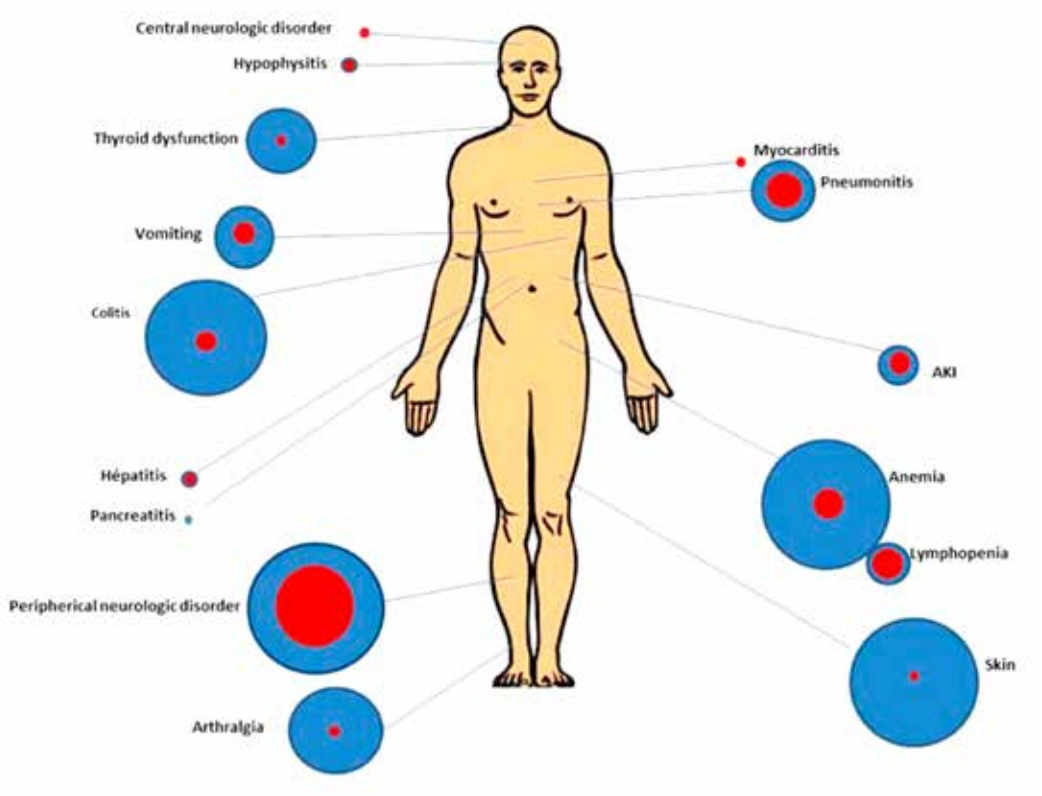

Figure 3[25] *Immunotherapy side effects*

patients with metastatic cancers who suffer from new tumors in different locations. Scientists have realized that an important challenge of immune and oncologic therapy results from the interaction of each patient's immune system and the cancer cell biology (or microenvironment). Researchers have discovered that cancer cells have over 11,000 genomic mutation differences from healthy cells surrounding the tumor.[24] Malignant cancers generally demonstrate immune evasion, which allows the cancer to proliferate and spread. Scientists have identified mechanisms where cancer cells coexist with the body's immune system. The most critical challenge for physicians is determining why some patients successfully respond to immunotherapy, while others are not sensitive to the treatments.

Treatment Side Effects

The immunotherapy and other cancer treatment options discussed each have distinct side effects. The most common risks and side effects are infections, skin rash, pain, swelling, nausea, fever, weakness, muscle aches, headache, dyspnea, hypotension, hypertension or heart palpitations. Physicians choose immunotherapy (sometimes multiple types) according to the type of cancer as well as the patient's overall health.

CONCLUSION

The standard of care for melanoma, kidney, and bladder solid tumors has been surgery combined with immunotherapy. Researchers have discovered that patient's biomarkers are predictive in determining the success of immunotherapy. Future studies are planned to understand tumor antigens, effector T cell functions and immune-suppressive mechanisms. The majority of physicians see a combined cancer treatment of chemotherapy and testing patient biomarkers to determine the individual's response to immunotherapy.

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Kassandra Bahr has been a Certified Surgical Assistant for 14 years since obtaining her associate degree of science in surgical technology. She has been a member of the neurosurgery team at Miami Valley Hospital, the region's only Level 1 Trauma Center. While employed at the hospital, Kassandra completed her master's and doctorate degrees in healthcare administration, and now splits her time between work as an online professor in the graduate program at Ohio University and as a Certified Surgical Technologist at Miami Valley Hospital.

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Use of Surgery and Immunotherapy to Treat Cancer

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1. **William Coley, known as the Father of Immunotherapy, experimented with the immune system in which cancer treatment:**
a. Bone cancer
b. Prostate cancer
c. Stomach cancer
d. All of the above

2. **Lloyd J. Old realized that cancer cells are unique and different than normal cells, and that this difference can be recognized by the human immune system.**
a. True
b. False

3. **Within the bloodstream, antibodies are blood protein produced by plasma cells as a response to counteract a/an:**
a. Antibody
b. Antigen
c. Tumor
d. Cell growth

4. **Antibodies work as follows:**
a. They may signal the immune system and trigger an attack
b. They may interfere with the cancer cell signal, attempting to grow, divide and spread
c. Both A and B
d. None of the above

5. **Once cancer cells begin to divide and spread in the body, the inflammatory response dampens the T Cell immune response, preventing autoimmunity.**
a. True
b. False

6. **Part of the monoclonal antibody process is to mark cancer cells, which helps the immune system _____ and _____ them.**
a. Identify and destroy
b. Divide and conquer
c. Multiply and subtract
d. Digest and absorb

7. **Type(s) of adoptive cellular therapy:**
a. Tumor-infiltrating lymphocyte (TIL)
b. Endogenous T cell (ETC) therapy
c. Chimeric Antigen Receptor (CAR) T cell therapy
d. All of the above

8. **Cytokine therapy uses two specific proteins to trigger the immune response:**
a. Soy and almond
b. Ferons and leukins
c. Cytokine and protokine
d. Interferons and interleukins

9. **Once the virus enters the cancer cells in oncolytic viral therapy, it begins to make copies of itself, which creates the following effect?**
a. This causes the cells to multiply and divide
b. This causes the cells to burst and die.
c. This causes the cells to die
d. This has no effect on the cells

10. **Cancerous tumors (lung, colorectal, liver, and breast) accounted for _____ deaths in 2016.**
a. 5 million
b. 100,000
c. 3.9 million
d. 8.8 million

USE OF SURGERY AND IMMUNOTHERAPY TO TREAT CANCER #443 NOVEMBER 2020 1.5 CE CREDITS $9

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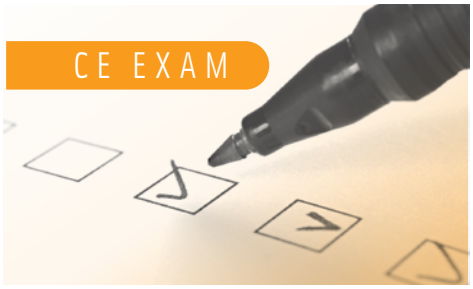

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