Lecture 17: Vaccines (Therapeutic and Prophylactic Types)

Therapeutic vaccines

Bacillus Calmette Guerin (BCG; TheraCys)

Very old agent initially developed as vaccine for mycobacterium tuberculosis (MTB).

Uses: Superficial bladder cancer (limited cancer spread); administered intravesically, directly into the bladder. Administered repetitively through an induction phase (once per week for 6 weeks), then in a maintenance phase at 3, 6, 12, 18, and 24 months following the first dose. Instilled directly into the empty bladder and allowed to remain for 2 hrs, then removed.

Mechanism: The BCG vaccine is made from a live, but attenuated bacterium strain (*Mycobacterium bovis*) which is related to human tuberculosis (TB) bacteria. The exact anti-cancer mechanism is not known, but when administered intravesically as a cancer therapy, BCG promotes a local acute inflammatory and sub-acute granulomatous immune reaction with macrophage and lymphocyte infiltration in the urothelium of the urinary bladder. It is unlikely that BCG attacks only cancer cells; the acute inflammatory/immune response kills lots of superficial cells (both normal and cancer cells).

Toxicities: Dysuria, urinary frequency, hematuria, fever.

Note(s): Initially developed as a vaccine against mycobacterium tuberculosis (*MTB*) and is still used in some parts of the world. Its overall effectiveness against *MTB* is controversial because some clinical results are positive, while other clinical results are negative.

Sipuleucel-T (Provenge); approved in 2010**;** Dendreon (formerly in Seattle)

Uses: For early (asymptomatic or minimally symptomatic) metastatic castrate resistant prostate cancer, also called hormone refractory prostate cancer. Not a commercial success for various reasons.

Mechanism: Classified as an autologous cellular immunotherapy and designed to induce an immune response targeted against PAP (prostatic acid phosphatase), an antigen expressed in most prostate cancers. The PAP antigen is amplified on antigen presenting cells (APCs).

Procedure (Figure 1):
1. Harvest blood cells from patient via standard leucopheresis 3 days prior to reinfusion date
2. Ship the cells to a special facility where the cells are cultured
3. Expose the cells to PAP-GM-CSF (PAP linked to GM-CSF); the APCs (antigen presenting cells) take up and process the recombinant target antigen into small peptides that are then displayed on the APC surface as a consequence of stimulation by GM-CSF
4. Ship the activated cells (sipuleucel-T) back to the clinic and then re-infuse into patient

Toxicities: Most common adverse events include chills, fatigue, fever, back pain, nausea, joint ache, and headache; rare but serious acute infusion reactions, cerebrovascular events.

Note(s): Because the therapy is an autologous cellular immunotherapy, each batch of the vaccine is actually unique to each patient. It's a living cell therapy.

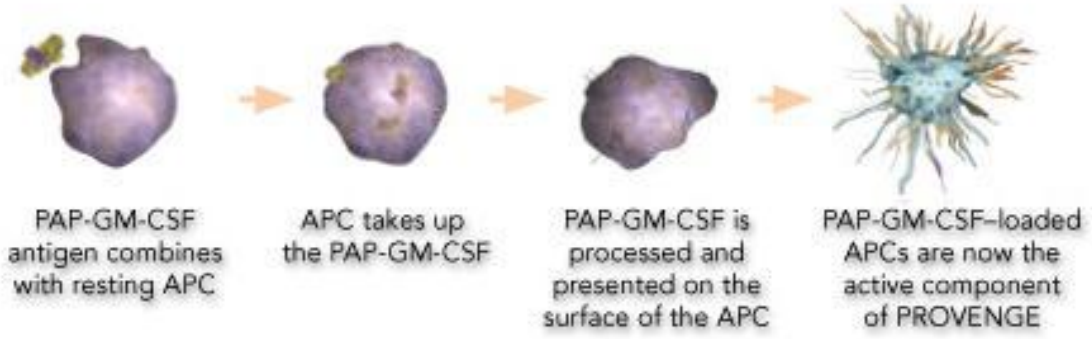

Figure 1. Activation of antigen presenting cells to generate sipuleucel T (Provenge)

~~Lapuleucel-T (**Neuvenge);** not yet approved (Dendreon)~~

~~Target use: Breast cancer, bladder cancer.~~

~~Mechanism: Immunotherapy to target tumor cells expressing HER2/neu (EGFR-2).~~

CAR-T cell therapy (chimeric antigen receptor - T cells)

These are T-cells that have been engineered to have new antigen receptors (chimeric) on their cell surfaces. These new receptors have the ability to recognize specific antigens that are present on tumor cells. These new receptors are chimeric because they can do two things: They recognize the tumor antigens and they activate the T-cells.

Procedure (Figure 2):
1. Harvest the T cells from patients
2. Genetically alter the T cells so they express the chimeric antigen receptors
3. Reinfuse the modified cells (CAR-T cells) back into patients to attack the cancer cells

In general, CAR-T cells can be either derived from T cells in a patient's own blood (autologous) or derived from the T cells of another healthy donor (allogenic). However, the initially approved

CAR-T therapies are both autologous. CAR-T cells are engineered to be specific to an antigen expressed on a tumor that has low expression on healthy cells.
After CAR-T cells are infused into a patient, they act as a "living drug" against cancer cells. CAR-T cells can help destroy/inhibit cancer cells through several mechanisms, including extensive stimulated cell proliferation thereby amplifying their effects, and by causing the increased secretion of factors that can affect other cells such as cytokines and interleukins.
Prior to reinfusion of CAR-T cells, patients are subjected to lymphodepletion in order to reduce the immune mediated rejection of the CAR-T cells.

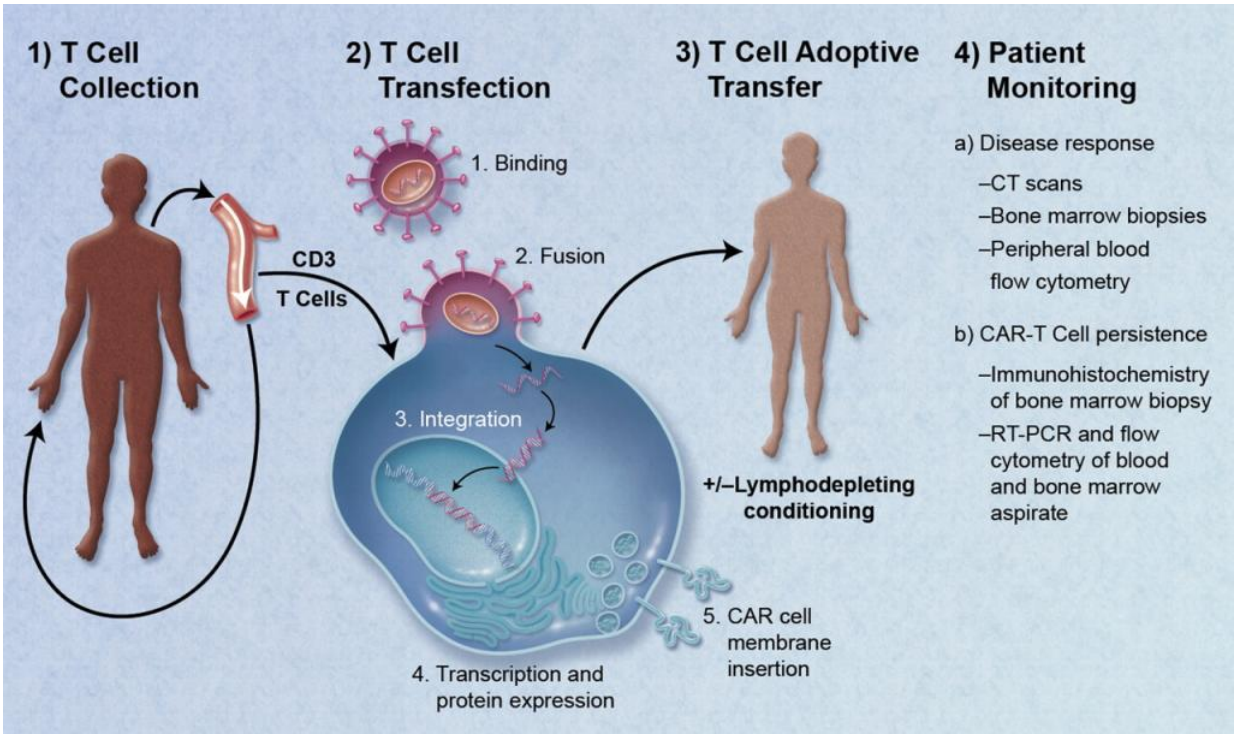

Figure 2. Steps for obtaining, modifying, and reinfusing CAR-T cells to a patient

Tisagenlecleucel (Kymriah): approved Aug, 2017 (autologous and IV only)

Uses: Approved for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Lymphodepleting chemotherapy: Fludarabine (30 mg/m² intravenous daily for 4 days) and cyclophosphamide (500 mg/m² intravenous daily for 2 days starting with the first dose of fludarabine). Infuse KYMRIAH 2 to 14 days after completion of the lymphodepleting chemotherapy.

Mechanism: Targets the **CD19** antigen, which is found on many types of B-cell cancers.

Toxicities: Cytokine release syndrome (CRS), neurotoxicity with CRS (all in black box); treat serious CRS with tocilizumab (Actemra) which is a MAB that targets cytokine IL-6.

Notes: Available only through the Kymriah REMS (Risk Evaluation and Mitigation Strategy).

Axicabtagene ciloleucel (Yescarta); approved Oct, 2017 (autologous and IV only)

Uses: Approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Lymphodepleting chemotherapy: Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously on the fifth, fourth, and third day before infusion of YESCARTA.

Mechanism: Targets the **CD19** antigen, which is found on many types of B-cell cancers.

Toxicities: Cytokine release syndrome (CRS), neurotoxicity with CRS (all in black box); treat serious CRS with tocilizumab (Actemra) which is a MAB that targets cytokine IL-6.

Notes: Available only through the Yescarta REMS (Risk Evaluation and Mitigation Strategy).

Prophylactic vaccines

Gardisil 9

Uses: Protection from infection by human papilloma viruses (HPV) that can cause cervical cancer in females and other forms of cancer in females and males (e.g. oral pharyngeal cancers); administered by multiple injections. First approved for females ages 9-26, then later approved for males ages 9-26. Very recently approved (Oct 2018), for both men and women age 27-45.

Mechanism: Targets two high risk HPV viruses (HPV-16 and HPV-18). HPV is known to cause cervical intraepithelial neoplasia (CIN) which is a precursor to cervical cancer. Also targeted against HPV-6 and HPB-11 that can cause genital warts, which boys get more than girls. Note: Gardisil-9 was approved in Dec 2014 and targets 9 HPV viruses for cancer (16, 18, 31, 39, 45, 52 and 58) and two for genital warts (6 and 11). Approved for females 9-26 and males 9-15.

Toxicities: Most are considered non-serious (e.g., fainting, pain and swelling at the injection site (arm), headache, nausea and fever). Fewer (<10%) are serious (death, permanent disability, life-threatening illness and hospitalization). There is no proven causal link between the vaccine and serious adverse effects; all reports are related by time only. However, they must be considered as "possibly related" to drug because the effect happened some time after the vaccination. There are also rare reports of a disorder called Guillen Barre Syndrome (GBS) occurring after the vaccinations. GBS is a neuromuscular disorder that causes muscle weakness. There is no solid scientific evidence suggesting that Gardasil causes or raises the risk of GBS. Finally, there have been rare reports of blood clots forming in the heart, lungs and legs.

Note(s): HPV is the most common sexually transmitted infection in adults in the world. Furthermore, it is estimated that most adults will have contracted at least one strain of HPV by age 50.

~~**Cervarix –** discontinued in late 2016 in the U.S.~~

~~Uses: Like Gardasil, protection from infection by human papilloma viruses (HPV); administered by injection as 3 doses (at 0, 1, and 6 months). Approved for females ages 9-25.~~

~~Mechanism: Targets two high risk HPV viruses (HPV-16 and HPV-18). HPV is known to cause cervical intraepithelial neoplasia (CIN) which is a precursor to cervical cancer. Vaccine also has cross-reactivity to two other HPV viruses (HPV-31 and HPV-45). Finally, it also contains AS04 (3-O-desacyl-4'- monophosphoryl lipid A), an adjuvant that boosts the immune system.~~

~~Toxicities: Fatigue, headache, myalgia, gastrointestinal symptoms, and arthralgia.~~

~~Note(s): A comparative clinical trial indicates that this agent is superior to Gardasil in terms of immune response to HPV, but does not protect from genital warts.~~
~~Both Gardisil and Cervarix are prophylactic vaccines, not therapeutic vaccines. Neither useful after an HPV infection is established.~~