Are you ready for the arrival of promising biological treatments like oncolytic immunotherapy? Prepare yourself or your staff during this presentation, which addresses the mechanism of action of oncolytic viruses, including cancer immunology, and potential adverse effects. You’ll learn how to develop a patient care plan that considers patient, public, and employee safety.

Content Area: Clinical Practice

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Full Disclosure:
Intends to discuss unapproved/investigational use of a commercial product/device during this educational activity

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Intends to discuss unapproved/investigational use of a commercial product/device during this educational activity

Objectives:
At the end of this session, participants will be able to:
1. Describe mechanism of action of oncolytic viruses.
2. Develop a care plan for a patient receiving oncolytic viruses.

Content Outline:
I. History of viruses as anti-cancer therapy
   A. Wild type
   B. Engineered
II. Mechanism of action
   A. Cytotoxic effect
   B. Immune response
      1. Innate
      2. Adaptive
         a. Neutralizing antibodies
III. Biosafety standards
   A. PPE
   B. Isolation
   C. Patient education
IV. Case presentation

Bibliography:
Department of Health and Human Services National Institutes of Health. (March 2013). NIH guidelines of research involving recombinant or synthetic nucleic acid molecules (NIH guidelines).


### History of Viruses as Anti-cancer Agents

**Why viruses?**

- Viruses infect individual cells
- Viruses use the DNA in cells to replicate
- Viruses lyse cells and release their progeny to surrounding cells
- Viruses stimulate the immune response

### Wild Type

- Virus as it occurs naturally
- Some viruses have low pathogenicity in their natural form
- Activate genetic anti-viral defense response
  - Protects cells from infection
  - Prevents spread
- Cancer cells have defects in the response
  - Unresponsive to interferons
  - Highly sensitive to infection
    - Causes death to malignant cells
    - Causes amplification (1000 fold) within 24hrs

### Genetically Engineered

- Attenuation of a virus by engineering a deletion
  - Deleting viral genes
  - Deleting gene regions
  - Eliminate viral functions that are expendable in tumor cells but not normal cells
  - Safer and more tumor-specific
- Ablates virtually all infection of normal tissues while replication within tumor cells is unaffected

### Wild Type vs. Genetically Engineered (example)

- Herpes simples virus wild type
  - Well understood
  - Relatively harmless \(\rightarrow\) cold sores
- Herpes simplex virus type-1 mutant 1716
  - Lacks ICP34.5 gene \(\rightarrow\) unable to replicate in non-dividing cells
  - Infects and lyses cancer cells
- Outer coating variants can be targeted to specific types of cancer cells
  - Can deliver additional genes to the cell
  - Decreases pathogenicity / increases selectivity
Increasing selectivity

- Transductional targeting
  - Modify the viral coat proteins
  - Target tumor cells
  - Reduce entry to non-tumor cells
  - To date mainly used on adenoviruses and HSV-1
- Non-transductional targeting
  - Altering the genome
  - Critical parts of genome require tumor-specific promoter
  - Only able to replicate in cancer cells
- Both are more effective than either one alone

Increasing oncolytic activity

- Viruses used as vectors:
  - Suicide genes
    - to deliver encoding enzymes that can convert non-toxic pro drug to a potent cytotoxin that diffuses to and kills neighboring cells
  - Antiangiogenic genes
    - Endostatin, angiostatin
  - Radio iodine
    - Causes infected tumor cells to accumulate iodine
    - Allows local radiotherapy

Review of the Immune Response

- Innate vs. Adaptive Immunity
- Innate
  - Cells and proteins always present and ready to mobilize and fight microbes at the site of invasion
  - Physical epithelial barriers
  - Phagocytic leukocytes
  - Dendritic cells
  - Natural killer (NK) cells
  - Circulating plasma proteins

Review of the Immune Response

- Innate vs. Adaptive Immunity
- Adaptive
  - Called into action when pathogens are able to evade or overcome innate immune defenses
  - Humoral immunity
    - B lymphocytes \( \rightarrow \) antibodies
  - Cell mediated immunity
    - T lymphocytes \( \rightarrow \) helper, cytotoxic

Review of the Immune Response

Innate:
- Immediate response but limited potency
- Recognizes general classes of pathogens
- Reacts with equal potency with repeated exposure to same pathogen

Adaptive:
- Slower response but very potent and long lasting
- Recognizes highly specific antigens
- Memory cells: more potent faster response on second exposure

Overcoming the Immune Response

- More of a problem with IV administration
  - Virus must survive blood complement and neutralizing antibodies
  - Immunosuppression and inhibition of complement enhance oncolytic viral therapy
  - Using uncommon human pathogens
  - Coating virus with polymer
  - Hide virus inside macrophages
Using the Immune Response

- Virus attracts attention of the immune system to the tumor
  - May help generate long-lasting antitumor immunity
  - Produces personalized cancer vaccine
  - Viruses delivering cytokines or other immune stimulating factors

Oncolytic Virus: Oversight in Clinical Trials

- Clinical trial oversight
  - Food and Drug Administration (FDA)
    - Good Clinical Practice (GCP)
    - IRB
  - Additional oversight for trials with oncolytic viruses
    - National Institute of Health (NIH) Guidelines
      - Recombinant DNA Advisory Committee (RAC)
      - Institutional Biosafety Committee (IBC)

Oncolytic Viruses: Safety Concerns

- What falls under the NIH guidelines?
  - Those with manipulation of DNA/RNA
- What are some of the considerations with respect to the virus?
  - Spectrum of disease caused by parental strain
  - Level of pre-existing immunity to parental virus in population
  - Ability of virus to evade immune response
  - Virus tropism

Oncolytic Viruses: Safety Concerns Continued

- What are some of the considerations with respect to those receiving or administering the virus?
  - Patient
    - Vertical and horizontal transmissions
  - Patient contacts
    - Family and friends
  - Health care providers
  - General public
  - Facilities and standard operating procedures (SOP)

National Institute of Health (NIH) Guidelines

- Specifies practices for constructing and handling
  - Recombinant nucleic acid and molecules
  - Synthetic nucleic acid molecules
  - Cells, organisms and viruses containing such molecules
  - Office of Biotechnology Activities (OBA)
    - Office within the NIH responsible for reviewing and coordinating all activities related to NIH
  - NIH Guidelines are mandatory if receiving NIH support

Recombinant DNA Advisory Committee (RAC)

- The NIH panel that oversees gene-therapy research in the U.S. established in 1974
- Membership
- Focus
  - Scientific, ethical & legal issues
- Recommendations go to NIH Director then thru OBA (office of biotechnology activities)
Institutional Biosafety Committee (IBC)

- Composition similar to RAC but with a non-voting site representative
- Qualifies a site
- Meet 1-2 times a month
- Site approval and annual review
- Independent of IRB

Biosafety in Microbiological and Biomedical Laboratories (BMBL)

- Risk criteria used to define the four levels of containment Biosafety levels 1-4 are:
  - Infectivity
  - Severity of disease
  - Transmissibility
  - Nature of the work being done

Biosafety Levels

- **Level 1 (BSL-1)**
  - Suitable for work involving well-characterized agents not known to consistently cause disease in immunocompetent adult humans
- **Level 2 (BSL-2)**
  - Suitable for work involving agents that pose moderate hazards to personnel and environment
- **Level 3 (BSL-3)**
  - Work performed with indigenous or exotic agents that may cause serious or potentially lethal disease through inhalation route exposure.
- **Level 4 (BSL-4)**
  - Work with dangerous and exotic agents that pose a high individual risk of life-threatening disease, aerosol transmission, or related agent with unknown risk of transmission

IBC site visit for Biosafety Level 2 Qualification

- Site visits
  - Initial site assessment
  - Annual review
  - Unscheduled
- Criteria
  - Training
  - Manuals
  - Reporting responsibilities
  - Spill and exposure plans
  - Employee health
  - Agent
  - Facility and equipment

Protocol Specific Biosafety SOP

- General Info on agent
- Personal protective equipment (PPE)
- Administration and PPE
- Shedding
- Handling and Storage
- Waste Handling
- Accidental Exposures
- Training Requirements

What if there’s an exposure?

- Containment
  - Close doors, spill kits
- Disinfect – fresh 10% bleach solution
- Looks at MSDS and/or Biosafety SOPs
- Notify supervisor
- Incident report
What can we expect in commercial market?

- FDA
- Industry
- Sites

Oncolytic Immunotherapy – Select Clinical Trials

- Onyx 015
- Oncocrine (H101)
- Coxsackievirus A21 (CAVATAK)
- HF10
- Talimogene Laherparepvec (T-VEC)
- JX-594 (Pexa-Vec)

Oncolytic Immunotherapy
ONYX-015

- Adenovirus engineered without E1B gene
  - E1B inhibits p53 activity
- Phase II trial 24 evaluable patients
  - 2 CR
  - 3 PR
  - 3 Minor
- Well tolerated
  - Fever
  - Injection site pain
- Confirmed replicating virus in tumor and not in normal tissue

Miller and Rickards, et al, 2009

Oncolytic Immunotherapy
ONYX-015

- Total 16 trials
- Head and neck, pancreatic, sarcoma, glioma, colorectal, ovarian and hepatobiliary
- 12/16 demonstrated objective responses or stable disease
- Fever most common side effect
- 3 trials with hepatotoxicity
- No systemic response

Nemunaitis et al, 2001
Senior, K., 2001

Oncolytic Immunotherapy
ONYX-015

- Weakness:
  - Immune response cleared virus too quickly
  - Adenoviruses are slow growing
  - Lost funding

Nemunaitis et al, 2001
Senior, K., 2001

Oncolytic Immunotherapy
Oncocrine (H101)

- First oncolytic viruses approved by China in 2005
  - Approved for Head and Neck Cancer
  - RR 79% H101 + chemo vs 40% chemo
- Larger deletion E1B gene
- Febrile response may enhance viral replication and tumor response

Yu and Fong, 2007
Oncolytic Immunotherapy

**CAVATAK**

- CAVATAK - Coxsackievirus A21
  - Live RNA virus from Enterovirus genus
  - Hand foot mouth disease
  - If infected mild respiratory infection
  - Propensity to replicate in cancer cells versus normal cells
  - Attaches to ICAM-1
  - Neutralizing antibodies in 14 days

www.viralytics.com
Hayes and Seigel, 2009.

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Oncolytic Immunotherapy

**HF10**

- HF10 is a spontaneously occurring attenuated mutant of Herpes Simplex virus Type 1.
  - N=28
  - Adverse events - Flulike symptoms
  - Rapid clearance from blood, urine and saliva
- HF10 sensitive to famcyclovir


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Oncolytic Immunotherapy

**JX-594 (Pexa-Vec)**

- JX-594 – Vaccinia virus
  - Used for small pox vaccine
  - Inactive thymidine kinase (TK) gene
  - Prevents replication in normal cells
  - Expressing granulocyte-macrophage colony-stimulating factor (GM-CSF)
    - Stimulate immune response
- Stable given in intravenous form
- Rapid replication and spread within tumors
- Proven safe in humans
  - Mild flu-like symptoms

Suvarna, 2013
Mulcahy, 2013

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Oncolytic Immunotherapy

**T-VEC**

- Talimogene laherporepvec – T-VEC
- Genetically modified HSV
  - Attenuated to support rapid growth in cancer cells
- Well tolerated
  - Flu like symptoms
    - Fatigue
    - Chills
    - Fever
    - Injection site pain

Suvarna, 2013
Mulcahy, 2013

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<td>12 month survival</td>
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Parato and Seigel, 2009
Oncolytic Immunotherapy

T-VEC

OPTIM Phase III randomized trial of Talimogene Laherparepvec (T-VEC) vs subcutaneous granulocyte-macrophage colony stimulating factor (GM-CSF) for the treatment of unresected stage IIIIB/C and IV melanoma

- N= 436 randomized 2:1
- Up to 4 ml T-VEC 10^6 first intratumoral injection then up to 4 ml 10^8 every 2 weeks
- Up to 10 tumors injected continued up to 24 injections

Suvarna, 2013
Mulcahy, 2013

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Suvarna, 2013
Mulcahy, 2013

Oncolytic Immunotherapy

Patient Care – Tumor Selection

- Tumor must be
  - Large enough to hold volume of viral agent
  - Away from large blood vessels
  - Accessible to injection

- Tumor Mapping
  - A visual tool to keep track of injected and non-injected tumors
    - Photos
    - Body Maps
    - Transparencies

Oncolytic Immunotherapy

Patient Care – Preparations

- PPE
- Topical anesthetics
- Cleansing
- Tumor injection
- Fanning
- Rotation of insertion site
- Dressings

Oncolytic Immunotherapy

Evaluation Criteria

- Immune Related Response Criteria
  - Developed to cover more patterns of response
    - Tumor shrinkage
    - Delayed response
    - Initial progression then response
    - New disease then response
  - Allows for initial growth and new lesions

Oncolytic Immunotherapy

Patient Care – Ethical and Social Issues

- Patient and family education
  - Isolation and contagion
  - Sexuality and birth control
**Oncolytic Immunotherapy Case Study**

- **SS a 56 year old white female**
  - April 2008 lesion on inner knee that started to change. Biopsy positive for melanoma.
  - Treatment
    - Wide local excision with lymph node sampling
      - 3 mm depth with one positive lymph node
      - T3b, N1b, M0 melanoma
    - Adjuvant interferon

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**Oncolytic Immunotherapy Case Study**

- **January 2012** a new nodule on left upper thigh biopsy positive for melanoma
  - BRAF mutation V600E
- **December 2012** 4 new nodules on upper thigh
- **Referred for clinical trial**
  - Enrolled in intra-tumoral oncolytic viral therapy
  - Currently without evidence of disease