IMMUNOTHERAPY
OVERVIEW

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Tom Baker Cancer Centre
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Faculty/Presenter Disclosure

- **Speaker**: Dr. Gloria Roldan Urgoiti

- **Relationships with commercial interests:**
  - Grants/Research Support: n/a
  - Speakers Bureau/Honoraria: n/a
  - Consulting Fees: AMGEN, Canadian Brain Tumor Consortium
  - Other: n/a
Disclosure of Commercial Support

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- Dr. Gloria Roldan Urgoiti is presenting at this Program on a voluntary basis.
- **Potential for conflict(s) of interest:** None
Mitigating Potential Bias

- Consultancy not related to this presentation topic.
General Objective

- Family Physicians will be able to identify the most common side effects associated with immunotherapy currently used and know when sending the patient to ED and/or contacting Medical Oncology is warranted.
SPECIFIC OBJECTIVES

- General overview of immune response in the context of cancer
- Understand the mechanism of action of checkpoint inhibitors.
- Review most frequent adverse events from these drugs.
IMMUNE RESPONSE

TYPES OF IMMUNOTHERAPY

Cancer Immunotherapy

Active

Specific

Vaccines
- Prophylactic (HPV, HBV etc.)
- Therapeutic (whole cancer cells, tumor lysates, dendritic cell vaccines)

Non-specific

Immune adjuvants (BCG, Imiquimod, Oncolytic virus)

Cytokines (IL-2, IL-12, GM-CSF, TNFα, Interferon α-2b etc.)

Passive

Immunomodulating antibodies

Adoptive Immunotherapy

WHAT ARE CTLA-4 and PD1/PDL1?
SIGNALS REGULATING T-CELLS

Activating Signals: CD28, OX40, GITR, CD137, CD27, HVEM
Inhibitory Signals: CTLA-4, PD-1, TIM-3, BTLA, VISTA, LAG-3

T-Cell Stimulation

T-Cell Inhibition

WHY THE IMMUNE SYSTEM DOES NOT ELIMINATE ALL CANCER CELLS?
**CHECKPOINT INHIBITORS**

**CTLA-4 mAbs:**
- Ipilimumab
- Tremelimumab

**PD-1 mAbs:**
- Nivolumab
- Pembrolizumab

**PD-L1 mAbs:**
- Atezolizumab
- Avelumab
- Durvalumab

…. If you take out the brakes…
IMMUNE-RELATED AES

- Ocular
  - Uveitis, episcleritis

- Pulmonary
  - Pneumonitis

- Hepatic
  - Increased liver function enzymes

- Pancreatic
  - Elevated lipase levels

- Infusion-related
  - Infusion-related reaction or hypersensitivity

- Endocrine
  - Hypothyroidism, hyperthyroidism, hypopituitarism, hypophysitis, adrenal insufficiency

- Dermatologic
  - Pruritus, rash, vitiligo, alopecia

- Renal
  - Nephritis, renal failure

- Gastrointestinal
  - Diarrhea, colitis, nausea

- General
  - Fatigue, headache, decreased appetite, arthralgia

Kreamer KM. J Adv Pract Oncol 2014
FREQUENCY - IPILIMUMAB

- Any iAEs: 64%
- Dermatologic: 45%
- Gastrointestinal: 32%
- Endocrine: 5%
- Pulmonary: 5%
- Hepatic: 2%

TIME OF ONSET

- Rash, pruritus
- Liver toxicity
- Diarrhea, colitis
- Hypophysitis

GRADE/GENERAL MANAGEMENT

- GRADE 1  - mild
- GRADE 2  - moderate
- GRADE 3  - severe
- GRADE 4  - life threatening
- GRADE 5  - death

Outpatient

Inpatient
DERMATITIS

Fig. 1 – Practical scheme for determining percentages of body surface area (BSA) affected by skin reactions in adults.

<table>
<thead>
<tr>
<th>Adult</th>
<th>Surface %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm</td>
<td>9</td>
</tr>
<tr>
<td>Head</td>
<td>9</td>
</tr>
<tr>
<td>Neck</td>
<td>1</td>
</tr>
<tr>
<td>Leg</td>
<td>18</td>
</tr>
<tr>
<td>Face/anterior trunk</td>
<td>18</td>
</tr>
<tr>
<td>Face/posterior trunk</td>
<td>18</td>
</tr>
</tbody>
</table>

Images online from L. Horn, Vanderbilt University.
- **GRADE 1** 10 continue

- **GRADE 2** 10-30 hold/delay - prednisone 1 mg/k/d

  oral antihistamines for pruritus

- **GRADE 3 - 4** > 30 Derm consult;

  Glucocorticosteroids i/v → infliximab or mycophenolate mofetil.
Toilet Paper Wedding Dresses
- 10% Grade 3-4 (7 or more stools above baseline, fever, ileus or peritoneal signs)
- 1% intestinal perforation
- 1% treatment related death

Hypothalamus

Indirect Control through Release of Regulatory Hormones

- Corticotropin-releasing hormone (CRH)
- Thyrotropin-releasing hormone (TRH)
- Growth hormone-releasing hormone (GH-RH)
- Growth hormone-inhibiting hormone (GH-IH)
- Prolactin-releasing factor (PRF)
- Prolactin-inhibiting hormone (PIH)
- Gonadotropin-releasing hormone (GnRH)

Regulatory hormones are released into the hypophyseal portal system for delivery to the anterior lobe of the pituitary gland.

Direct Release of Hormones

- Sensory stimulation
- Osmoreceptor stimulation

Adrenal cortex

- ACTH

Adrenal glands

- Glucocorticoids (steroid hormones)

Thyroid gland

- TSH
- GH

Liver

- PRL

Somatomedins

Bone, muscle, other tissues

Mammary glands

- Testes of male

Melanocytes (uncertain significance in healthy adults)

- Inhibin
- Testosterone
- Estrogen
- Progesterone
- Inhibin

Females: Uterine smooth muscle and mammary glands

Males: Smooth muscle in ductus deferens and prostate gland
- Hypophysitis 9%
- Adrenal insufficiency 5%
- Hypothyroidism 7-22%
Headache
Visual changes
Nausea/vomiting

Secondary adrenal insufficiency

<table>
<thead>
<tr>
<th>LAB RESULT</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST or ALT $\leq 2.5 \times$ ULN</td>
<td>GRADE 1</td>
</tr>
<tr>
<td>BT $\leq 1.5 \times$ ULN</td>
<td></td>
</tr>
<tr>
<td>AST or ALT 2.5-5 $\times$ ULN</td>
<td>GRADE 2</td>
</tr>
<tr>
<td>BT 1.5 – 3 $\times$ ULN</td>
<td></td>
</tr>
<tr>
<td>AST or ALT $&gt; 5 \times$ ULN</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>BT $&gt; 3 \times$ ULN</td>
<td></td>
</tr>
</tbody>
</table>

*hepatology / gastroenterology consultation +/- liver biopsy*
COUGH AND FEVER!

DRUG VS BUG
**HYPOXIA**

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Radiographic changes only)</td>
<td>(Mild-to-moderate symptoms; worsens from baseline)</td>
<td>(Severe symptoms; new/worsening hypoxia; life-threatening); <strong>hospitalize</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment With OPDIVO or OPDIVO + YERVVOY Regimen</th>
<th>Consider withholding treatment</th>
<th>Withhold treatment</th>
<th>Permanently discontinue treatment</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Every 2 to 3 days</th>
<th>Daily</th>
<th>Daily</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Consult</th>
<th>Consider pulmonary and infectious disease</th>
<th>Pulmonary and infectious disease</th>
<th>Pulmonary and infectious disease</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Steroids</th>
<th>-</th>
<th>1-2 mg/kg/day prednisone equivalents</th>
<th>1-2 mg/kg/day prednisone equivalents†</th>
</tr>
</thead>
</table>

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<tr>
<th>Pulmonary Tests</th>
<th>-</th>
<th>Consider bronchoscopy, lung biopsy</th>
<th>Consider bronchoscopy, lung biopsy</th>
</tr>
</thead>
</table>
Autoimmune pneumonitis complicating immunotherapy for metastatic melanoma with checkpoint inhibition
PROGRESSION OR PSEUDOPROGRESSION?

PSEUDO-

means

False

by acronymsandslang.com
Response to immune checkpoint inhibitor treatment with brief increase in tumor size (pseudoprogression)

- Pseudoprogression

Tumor Size

Activated T cells enter tumor

Start of treatment

Time

- Tumor cell
- T cell

West HJ. JAMA Oncol. 2015;1:115.
Delayed response to ipilimumab therapy

Pre-treatment

Week 12 (10/06)

4 blind doses ipilimumab

No drug

12/06

5/07

4 10 mg/kg dose ipilimumab
The most used modality of immunotherapy currently involve checkpoint inhibitors = antibodies against CTL-4, PD1 and PDL1.

From inhibiting inhibitory mechanisms you expect “uncontrolled” T-cell response that can affect ANY organ.

Holding agent +/- corticosteroids = treatment

Specially for colitis and neumonitis ddx: infection!
TAKE HOME MESSAGES 2/3

- AES from immunotherapy can be as/more severe than those from chemotherapy
- Patients are very close monitored including pauci-symptomatic AEs.
- SEVERE = ADMISSION
- Prolonged moderate → admission; so call your friend the oncologist.
TAKE HOME MESSAGES 3/3

- Other types of immunotherapy in experimental phases or in isolated centres (US).
- Standard of care:
  - melanoma
  - non-small cell lung cancer
  - kidney cancer
  - bladder cancer
  - head and neck cancers
  - Hodgkin lymphoma
- ++++ in clinical trials
SPECIFIC OBJECTIVES

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Thank you.