Do you know the promising potential of indoleamine (IDO) in the treatment of solid tumors and hematological malignancies? In this session, you’ll delve into the role of this immunoregulatory metabolic enzyme in immunosuppression, tumor progression, and symptom expression. You’ll review the genetic polymorphisms associated with IDO expression, the influence of IDO on tryptophan catabolism and regulatory T lymphocyte function, and clinical trials of IDO inhibitors. The effects of IDO on symptom development via tryptophan will also be explored.

Content Area: Clinical Practice

Content Level: Advanced

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Objectives:
At the end of this session, participants will be able to:
1. Describe the role of IDO in immunosuppression, tumor progression, and symptom expression.
2. Generate possible clinical applications of IDO inhibitors in cancer treatment.
3. Identify symptoms that might be experienced by patients receiving IDO inhibitors.

Content Outline:
I. Indoleamine 2,3-dioxygenase (IDO) and immune regulation
   A. Tryptophan catabolism
   B. T-cell proliferation

II. IDO and cancer progression
   A. Biological effects of IDO
   B. Cancers associated with IDO
   C. Genetic polymorphisms associated with IDO expression

III. Use of IDO inhibitors in cancer treatment
   A. Biological effects of IDO inhibition
      1. Tumor suppression
      2. Symptom production
   B. IDO inhibitors
   C. Pre-clinical studies
   D. Clinical trials
   E. Combination therapies
   F. Symptom production

IV. Nursing implications
   A. Patient care and education
   B. Nursing research

Bibliography:
Polyphenols inhibit indoleamine 3,5-dioxygenase-1 enzymatic activity—a role of immunomodulation in chemoprevention. *Discovery Medicine, 14*, 327-333.


Indoleamine 2,3-dioxygenase (IDO)

- Immune regulation
  - Tryptophan catabolism
  - T-cell proliferation
  - T-cell function
  - T-cell survival
- Cancer Progression
  - Biological effects of IDO
  - Cancers associated with IDO
  - Genetic polymorphisms associated with IDO expression

IDO and Cancer

- To survive, tumors escape normal immune surveillance by inducing tolerance and suppressing normal immune responses
- IDO is an immune suppressant, specifically suppressing T-cell dependent anti-tumor immunity
- Cancer cells express IDO

Cancers Associated with IDO Expression

- High IDO Expression
- Poor Outcomes
  - Ovarian cancer
  - AML
  - Endometrial cancer
  - Colon cancer
  - Malignant melanoma
  - Hepatocellular carcinoma

IDO Inhibitors

- Competitive inhibitors
  - 1-Methyl-D-Tryptophan
  - 1-Methyl-L-Tryptophan
- Small molecule inhibitors
  - Naphtoquinones
  - Epigallocatechin gallate
  - Rosmarinic acid
  - p-Coumaric acid
- Gene Silencing by siRNAs
  - Epigallocatechin gallate
  - Rosmarinic acid
  - p-Coumaric acid
- Chemical Inhibitors
  - Methylthiohydantoin tryptophan
  - S-Br-Brassinin
- Cox-2 inhibitors

Pre-clinical Studies

Improved immune surveillance of cancer cells by T-cells may be most effective when combined with other therapies

- Chemotherapy
- Immunotherapy

1-Methyl-D-Tryptophan (D-1MT)

- Competitive IDO inhibitor – low potency
- Suppressed premalignant colon lesions in rats
- Synergistic (in mouse mammary tumors) with
  - Alkylating agents
    - Cisplatin
    - Cyclophosphamide
  - Antineoplastic antibiotics
    - Doxorubicin
  - Taxane mitotic inhibitors
    - Paclitaxel

Muller et al., Nature Medicine, 2005.
Ogawa et al., Cancer Science, 2012.

1-Methyl-D-Tryptophan (D-1MT)
• D-1MT does not increase efficacy (in mouse mammary tumors) of
  – Antimetabolites
    • 5-Fluorouracil
    • Methotrexate
  – Mitotic inhibitors (Vince alkaloids)
    • Vinblastine
  – Signal transduction inhibitors
    • FTI
    • Rapamycin
  – Antiangiogenics
    • Tetrathiomolybdate

Muller et al., Nature Medicine, 2005.

1-Methyl-L-Tryptophan (L-1MT)
• Less effective than D-1MT for enhancing anti-tumor responses in vivo
• May be able to replace tryptophan depleted by IDO

Schmidt et al., Public Library of Science one, 2012.

Other Mechanisms of 1MT
• D and/or L-1MT may effect tumor growth by other mechanisms than IDO inhibition
  – Direct T-cell stimulation
  – Modulation of dendritic cell function
  – Reverse the transformation of CD4+ T cells to T_{Reg}
  – Interference with protein expression
• IDO inhibitors may also promote tumor growth


Naphthoquinone-Based Inhibitors
• Naphthoquinone core – binding structure
• Annulin B – natural product of marine hydroid
• Menadione (Vitamin K3) – natural product
• Pyranonaphthoquinones – synthetic products in development; potent IDO inhibitors


Menadione (Vitamin K3)
• Radiosensitizer
• Synergistic with Vitamin C
• Shown to increase sensitivity to many chemo agents in a variety of cancers
  – 5FU
  – Bleomycin
  – Cisplatin
  – Dacarbazine
  – Mercaptopurine
  – Cytarabine
  – Hydroxurea
  – Thiopeta
  – Doxorubicin
  – Mitoxanthine
  – Mitomycin C
  – Actinomycin D
  – Vincristine
  – Vinblastine
  – Etoposide
  – Methotrexate


Exiguamine A
• Natural alkaloid from a marine sponge
• Potent IDO inhibitor
• In development

Epigallocatechin Gallate (EGCG)

- Natural product of green tea
- Suppressed premalignant colon lesions in rats

Ogawa et al., Cancer Science, 2012.

Rosmarinic Acid (RA)

- Natural fraction of herb Summer Savory
- Suppresses expression of IDO in dendritic cells
- Also has anti-oxidant and anti-cyclooxygenase properties
- Protects nephrons from cisplatin damage

Bhatt et al., Drug Delivery, 2013.
Domtravil et al., Food and Chemical Toxicology, 2014.
Lee et al., Biochemical Pharmacology, 2007.

p-Coumaric Acid (CA)

- Natural product of plants and foods, such as peanuts, tomatoes, garlic, wine, honey, flaxseed
- Anti-oxidant
- Suppresses IDO expression by dendritic cells

Kim et al., International Pharmacology, 2007.

Methylthiohydantoin Tryptophan (MTH-trp)

- Necrostatin-1
- Suppresses IDO induction by IFN-c at the transcriptional level

Okamoto et al., Cytotechnology, 2007.
Takahashi et al., Cell death & Disease, 2012.

5-Br-Brassinin

- Tumor cells suppressed by single agent treatment
- Tumor regression in combination with paclitaxel

Banerjee et al., Oncopune, 2008.

Cox-2 Inhibitors

- Celecoxib with dendritic cell-base cancer vaccine in mouse mammary tumors – reduced tumor size, prevented metastasis, increased survival
- Nimesulide down-regulated IDO expression in human AML cells
- Celecoxib decreased tumor size and metastasis in mouse lung cancer

Basu et al., Journal of Immunology, 2006.
Iachininoto et al., Molecules, 2011.
Lee et al., Journal of Immunotherapy, 2009.
Clinical Studies

- **D-1MT (Indoximod)**
  - Phase 1 – metastatic solid tumors – completed 1/2013 – results not yet reported
  - Phase 1 – inoperable metastatic or refractory solid tumors – completed 9/2013 – results not yet reported

[http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Combination with Radiation Therapy

- **Menadione**
  - Phase 1/2 – with radiation therapy in inoperable lung cancer


Combination with Chemotherapy

- **Menadione**
  - Phase 1 with mitomycin C in refractory solid tumors
  - Phase 2 with mitomycin C in advanced gastrointestinal cancer
  - Phase 2 with mitomycin C in lung cancer
- **D-1MT (Indoximod)**
  - Phase 1 – with docetaxel in metastatic solid tumors
  - Phase II Double-Blinded, Randomized, Placebo-Controlled Study - with docetaxel in metastatic breast cancer
  - Phase I/II – with temozolomide for temozolomide-refractory primary malignant brain tumors

[http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Combination with Anti-cancer Vaccines

- **D-1MT (Indoximod)**
  - Phase 1/2 – with AD.p53 DC vaccine in invasive breast cancer and metastatic solid tumors – ongoing – completion 12/2014
  - Phase 2 - randomized, double blind, placebo-controlled after completion of standard sipuleucel-T in metastatic hormone refractory prostate cancer – recruiting – completion 12/2014

[http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Potential Side Effects from IDO Inhibition

- Infection – particularly opportunistic
- Hemolysis, hemolytic anemias, low blood counts
- Graft rejection
- Miscarriage, teratogenicity
- Autoimmune disease and allergic exacerbations

Van der Marel et al. *Journal of Immunology*, 2007.

Symptoms that may be helped by IDO inhibition

- Fatigue
- Depression
- Lack of appetite
- Sleep disturbance
- Drowsiness
- Cognitive dysfunction
- Peripheral neuropathy
- EGFR inhibitor rash

Moreno et al., *Federation of European Biochemical Societies Journal*, 2013.
Muller, *Current Opinion in Investigational Drugs*, 2010.
[http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)
Patient Care and Education

- WE REALLY DON’T KNOW
- Assess for signs of infection
- Teach patient to avoid infections and to report symptoms promptly
- Instruct female patients to avoid becoming pregnant
- Do not allow pregnant women to have contact with iDO inhibitors
- Do not administer to solid organ transplant recipients
- Monitor blood counts
- Obtain history of autoimmune diseases and allergies – administer with caution in patients with a positive history
- Warn patients about exacerbations of allergy symptoms
- Warn patients about exacerbations of allergy symptoms
- Menadione – contraindicated for patients on warfarin therapy

Nursing Research

- Identify symptom changes associated with new therapies
  - Symptoms caused by therapies
  - Expected and unexpected symptom benefits from therapies
- Advocate to include symptom identification studies beginning with Phase I clinical trials
  - Initial qualitative studies to obtain in depth report of patient experience
  - Develop and test quantitative instruments in larger numbers of patients in Phase II and III trials
- Studies to develop evidence for therapy management beginning in Phase II and III trials