1 Role of PARP Inhibitors in Metastatic Breast Cancer
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2 Disclosure:
  - I have nothing to disclose.

3 Objectives:
  - Describe poly-ADP-ribose polymerase (PARP) inhibitors mechanism of action.
  - Evaluate PARP inhibitor role in treatment for BRCA1/2+ metastatic breast cancer.
  - Review a patient case of metastatic breast cancer.
  - Apply available literature to clinical practice.

4 Topic Selection:
  1) Cancer Center
  2) Angelina Jolie Effect (2013)
     - BRCA1 +
     - Mother died at 56 from breast cancer
     - 87% risk of breast cancer
     - 50% risk of ovarian cancer
     - Surgery = risk reduced to 5%

5 BRCA Genes:

  - Produce proteins that act as tumor suppressor proteins
    - Repair DNA by homologous recombination
  - Gene Mutations: Altered proteins or prevent creation of proteins
    - Deficient in repair
    - Accumulation in genetic mutations → Cancer
Highly Penetrant Gene Mutations:
- Inherited in a dominant fashion
  - **BRCA 1/2**
    - Breast (Males and Females), Ovarian, Prostate, Pancreatic
  - TP53
    - Breast, osteosarcoma, leukemia, brain tumors
  - PTEN
    - Breast, endometrial, thyroid
  - MSH2, MLH1, MSH6, PMS2, EPCAM
    - Colorectal, endometrial, ovarian, pancreatic, stomach
- Suggestive of Hereditary Cancer:
  - Early age onset, bilateral cancers, unusual cancers (male breast), multiple generations, cancers with birth defects

The Angelina Effect
- Not all patients with cancer-predisposing mutations will develop cancer
  - Variable Coverage
  - Private>Public>Uninsured
  - With Cancer > Without Cancer

Patient Case
- 54 year old white, female
- Diagnosis:
  - 2002: invasive right breast cancer
  - 2012: BRCA 2 mutation
  - 2014: metastatic breast cancer
    - Multiple pulmonary and paraesophageal nodules

Patient Case Continued:
- Breast cancer, GERD, seasonal allergies
- Bilateral mastectomy with implants, Bilateral salpingo-oophorectomy
- Mother (81 y.o.): BRCA 2 mutation: colon cancer
- Sisters: 2/4 sisters have BRCA 2 mutation
  - *One sister negative, one not tested
  - (-) alcohol or tobacco, works 4PM-7AM
Omeprazole 40 mg daily, prochlorperazine 10mg PRN nausea/vomiting, lorazepam 1mg PRN anxiety
- Weight: 66.9 kg, BP 122/72 mmHg, HR 100 bpm, afebrile

**HR 1 Positive Test Results:**
00 bpm, afebrile

- Human Epidermal Growth Factor Receptor (HER) Family
  - Treatments: trastuzumab (Herceptin), ado-trastuzumab emtansine (Kadcyla), neratinib (Nerlynx), pertuzumab (Perjeta), lapatinib (Tykerb)
- Estrogen Receptors (ER) and Progesterone Receptors (PR)
  - “Hormone sensitive”
  - Treatments: tamoxifen, anastrazole, exemestane, letrozole, fulvestrant (Faslodex), goserelin (Zoladex), leuprolide (Lupron)

**Patient Case Continued:**

- Metastatic breast cancer Testing Results:
  - ER (+)
  - PR (+)
  - HER2 (-)
- 2002: Chemotherapy
  - doxorubicin and cyclophosphamide
- 2002 - 2007: Tamoxifen
- Post 2007: Everolimus and Letrozole

**HER2 Negative Treatment**

**HER2 Negative Treatment:**

- Poly-ADP-ribose polymerase (PARP)
  - DNA repair enzyme found in repair pathways
    - Nucleotide excision repair
    - Single-strand break repair

**FDA Approval of PARP-Inhibitors:**

- Originally 3rd and 4th line treatments
  - Expanded to prior chemotherapy (>3 or platinum based agents)
The Cell Cycle:
- PARP enzyme predominantly working during:

PARP Inhibitors MOA:
- Part 1: Inhibiting PARP Enzyme
- Part 2: PARP Enzyme Trapping
- Part 3: Multimodal

Part 1:
- Molecular mimics of nicotinamide: compete with NAD+
  - Bind within NAD+ binding site

- Prevents PARylation → Prevents recruitments of repair proteins

Differ from topoisomerase inhibitors that directly target DNA-protein via covalent bond → noncovalent bond at active site on PARP enzyme

- Interfere with identification of DNA damage for repair
- = Accumulation of unrepaired DNA breaks

Part 1:
Synthetic Lethality: Cell death as result of deficient expression of two or more genes
Part 2:
- PARP-Trapping: PARP-DNA complex at site of DNA damage
  - "PARP Poison"

How: inhibitor-induced reverse-allosteric signaling

Bottom Line: Trap PARP enzymes on their DNA repair sites
- Prevents dissociation of PARP from DNA
  - Required for repair completion

- Ability to PARP-Trap varies between PARP inhibitors
  - Does not correlate with potency of PARP enzyme inhibition

Evidence:

OlympiAD Trial: olaparib (Lynparza)
New England Journal of Medicine
August 2017

Question: What is the efficacy and safety of olaparib compared to standard chemotherapy of physicians choice for the treatment of metastatic breast cancer (HER2 Negative) and BRCA mutation?

- Open-label, randomized, multicentered, international phase 3 trial:
  - 2:1 ratio

  olaparib 300mg twice daily

Single-agent:
(21 day cycles)

Capecitabine %
Eribulin %
Vinorelbine %
Figure 1A: Results

- The primary outcome of progression-free survival or death was longer in the olaparib group compared to the standard therapy group, 7.0 months vs. 4.2 months respectively.

Results OlympiAD Trial: olaparib (Lynparza)

- OlympiAD Trial: olaparib was associated with longer progression-free survival than standard therapy
  - Risk of disease progression or death 42% lower with talazoparib than with standard therapy
    - HR, 0.58; 95% CI, 0.43 to 0.80, P<0.001
  - Similar results as EMBRACA Trial: risk of disease progression or death 46% lower with talazoparib than with standard therapy
    - HR, 0.54; 95% CI, 0.41 to 0.71

Figure 3: Results

Results OlympiAD Trial: olaparib (Lynparza)

- Secondary Endpoint:
  - Overall Survival was not statistically different between the two groups.

  Median Time to death:
  - Olaparib = 19.3 months
  - Standard therapy = 19.6 months
HR, 0.90; 95% CI, 0.63 to 1.29, P= 0.57

32 Figure 1B: Results

33 Side Effects olaparib (Lynparza):
- Most common: anemia
  - Grade 3 - 4 hematologic adverse effects in 55% talazoparib vs. 38% standard therapy
  - Hgb: <8 - 6.5 g/dL (transfusion indicated)
- Thrombocytopenia
- Neutropenia
- Mild-to-moderate fatigue
- Nausea

34 Patient Case Continued:
- Initial metastatic treatment:
  - 2014 - 9/2018: Carboplatin AUC of 5
  - Stabilization and response for ~3 years

- 9/2018: CAT Scan of chest
  - Known paraesophageal lymph node 1.5 cm in 2017 → Grew to 2.9 x 2.8 cm
  - Breast cancer progression
- 10/2018: Olaparib (Lynparza) 300mg BID

35 Patient Case Continued:
- Most Recent Office Visit:
  - Increased nausea and vomiting
Occasional headaches
- Dizziness (1 episode)
- Chronic cough (unchanged)
- Dyspnea on exertion
- Significant appetite decrease
- Denies diarrhea, dysuria, fevers

36 Side Effects and Counseling Points PARP Inhibitors:
- Risk of bone marrow complications during or after treatment:
  - Myelodysplastic Syndrome (MDS)
  - Acute Myeloid Leukemia (AML)
- Low blood counts can be symptoms of treatment or MDS/AML
  - Contact Provider:
    - Weakness, weight loss, fever, blood in stool/urine, bruises, shortness of breath

Other Side Effects to Expect:
- Loss of appetite
- Headache, fatigue, nausea, vomiting, diarrhea
- Hair loss

37 Patient Case Continued:
- Most Recent Office Visit:
  - During first two weeks of therapy patient reports only taking 150mg BID

38 Administration olaparib (Lynparza):
Supplied: 100mg or 150mg capsules or tablets
*Note dosing to patients
- Can take with or without food
- Swallow whole: do not open, crush, dissolve, chew
- Vomiting or misses a dose: do not take an additional dose, take next dose at scheduled time
• Do not take if pregnant: embryo-fetal harm
  o No human data: animal studies only
  o No pediatric data

• Store at room temperature

39 Patient Case Continued:

• Most Recent Office Visit:
  o Increased nausea and vomiting

Treatment:
• In clinic:
  o IV fluids, ondansetron, and famotidine

• Hold olaparib dose for 1 day

• Prescription: ondansetron 8mg twice daily

• CT scans scheduled for January

40 Future:

• PARP Inhibitors vs. Platinum-Based therapy
  o Results from Negative Breast Cancer Trial showed response to carboplatin 68% vs. 33% with docetaxel
    ■ 43 patients w/ Triple negative Breast Cancer + BRCA mutation
  o Response rate to cisplatin 80% (20 patients BRCA mutation)

• PARP Inhibitors + Monoclonal Antibodies
  o Bevacizumab (Avastin)

• Head-to-Head Comparison of PARP Inhibitors

41 Future Efficacy Enhancements:
• Proposed for Triple Negative Breast Cancers and Acute Myeloid Leukemia (AML)
• DNMT Inhibitors (DNA methyltransferase) = 5-azacytidine, decitabine
- Altered cytosine base + covalently bind DNMT
- DNMT-DNA Complex + degrade DNMT enzyme

Questions?

Text attendance code to 413-200-2444
Code: SENFUV

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