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

6 **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

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7 **The Angelina Effect**

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

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8 **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

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- 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, prochlorperzine 10mg PRN nausea/vomiting, lorazepam 1mg PRN anxiety
- Weight: 66.9 kg, BP 122/72 mmHg, HR 100 bpm, afebrile
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10 **HR 1Positive 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)
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11 **Patient Case Continued:**

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

13 **HER2 Negative Treatment:**

- Poly-ADP-ribose polymerase (PARP)
  - DNA repair enzyme found in repair pathways
    - Nucleotide excision repair
    - Single-strand break repair
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14 **FDA Approval of PARP-Inhibitors:**

- Originally 3rd and 4th line treatments
  - Expanded to prior chemotherapy (>3 or platinum based agents)

15 **The Cell Cycle:**

- PARP enzyme predominantly working during:

16 **PARP Inhibitors MOA:**

Part 1: Inhibiting PARP Enzyme

Part 2: PARP Enzyme Trapping

Part 3: Multimodal

17 **Part 1:**

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

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- Molecular mimics of nicotinamide
- NAD+ within PARP enzyme

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- Prevents PARylation ⟶ Prevents recruitments of repair proteins

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

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

22 **Part 1:**

Synthetic Lethality: Cell death as result of deficient expression of <u>two or more</u> genes

23 **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

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- Multimodal cellular response
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25 **Evidence:**

26 **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?

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

olaparib 300mg twice daily

Single-agent:
(21 day cycles)

Capecitabine %
Eribulin %
Vinorelbine %

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28 **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.

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29 **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

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30 **Figure 3: Results**

31 **Results OlympiAD Trial: olaparib (Lynparza)**

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

Median Time to death:

- Olarparib = 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

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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
  - No human data: animal studies only
  - No pediatric data
- Store at room temperature

39 **Patient Case Continued:**

- Most Recent Office Visit:
  - Increased nausea and vomiting

Treatment:

- In clinic:
  - 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
  - Results from Negative Breast Cancer Trial showed response to carboplatin 68% vs. 33% with docetaxel
    - 43 patients w/ Triple negative Breast Cancer + BRCA mutation
  - Response rate to cisplatin 80% (20 patients BRCA mutation)
- PARP Inhibitors + Monoclonal Antibodies
  - 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

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- Questions?

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