Breast Cancer in Patients with BRCA1/2 mutations

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What distinguishes BRCA1/2 associated breast cancer?

• Younger age at diagnosis
• Imaging – better visualized on MRI
• Amongst women being screened– often interval cancers
• Distinct histo-pathological features
• Bilaterality
<table>
<thead>
<tr>
<th>Age at BC diagnosis</th>
<th>N</th>
<th>carriers</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>dx 20-29</td>
<td>11</td>
<td>3</td>
<td>27%</td>
</tr>
<tr>
<td>dx 30-39</td>
<td>74</td>
<td>18</td>
<td>24%</td>
</tr>
<tr>
<td>dx 40-49</td>
<td>245</td>
<td>29</td>
<td>11.8%</td>
</tr>
<tr>
<td>dx 50-59</td>
<td>345</td>
<td>33</td>
<td>9.5%</td>
</tr>
<tr>
<td>dx &gt;60</td>
<td>368</td>
<td>27</td>
<td>7.3%</td>
</tr>
</tbody>
</table>
IMAGING FOR SCREENING AND DIAGNOSIS IN BRCA1/2
Screening & Diagnosis:
MRI in women with high risk of breast cancer

Exclusively BRCA+ cohort

<table>
<thead>
<tr>
<th></th>
<th>The Netherlands</th>
<th>Canada</th>
<th>United Kingdom</th>
<th>Germany</th>
<th>United States</th>
<th>Italy</th>
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</thead>
<tbody>
<tr>
<td>No. of centers</td>
<td>6</td>
<td>1</td>
<td>22</td>
<td>1</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>No. of women</td>
<td>1,909</td>
<td>236</td>
<td>649</td>
<td>529</td>
<td>390</td>
<td>105</td>
</tr>
<tr>
<td>Age range</td>
<td>25–70</td>
<td>25–65</td>
<td>35–49</td>
<td>≥30</td>
<td>≥25</td>
<td>≥25</td>
</tr>
<tr>
<td>No. of cancers</td>
<td>50</td>
<td>22</td>
<td>35</td>
<td>43</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Sensitivity (%) MRI</td>
<td>80</td>
<td>77</td>
<td>77</td>
<td>91</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Sensitivity (%) Mammogram</td>
<td>33</td>
<td>36</td>
<td>40</td>
<td>33</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Sensitivity (%) Ultrasound</td>
<td>n/a</td>
<td>33</td>
<td>n/a</td>
<td>40</td>
<td>n/a</td>
<td>16</td>
</tr>
<tr>
<td>Specificity (%) MRI</td>
<td>90</td>
<td>95</td>
<td>81</td>
<td>97</td>
<td>95</td>
<td>99</td>
</tr>
<tr>
<td>Specificity (%) Mammogram</td>
<td>95</td>
<td>&gt;99</td>
<td>93</td>
<td>97</td>
<td>98</td>
<td>0</td>
</tr>
<tr>
<td>Specificity (%) Ultrasound</td>
<td>n/a</td>
<td>n/a</td>
<td>91</td>
<td>91</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

n/a = not applicable.

Sensitivity = \( \frac{\text{number of true positives}}{\text{number of true positives + number of false negatives}} \)

Specificity = \( \frac{\text{number of true negatives}}{\text{number of true negatives + number of false positives}} \)

- sensitivity = probability of a positive test given that the patient has the disease
- specificity = probability of a negative test given that the patient is well

American Cancer Society Guidelines, 2007
Screening & Diagnosis: MRI in women with high risk of breast cancer

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Rates of Detection and Follow-up Tests for Screening MRI Compared with Mammography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td>The Netherlands</td>
</tr>
<tr>
<td>Positives</td>
<td>13.7%</td>
</tr>
<tr>
<td>Recalls</td>
<td>10.84%</td>
</tr>
<tr>
<td>Biopsies</td>
<td>2.93%</td>
</tr>
<tr>
<td>Cancers</td>
<td>1.04%</td>
</tr>
<tr>
<td>False negatives</td>
<td>0.23%</td>
</tr>
</tbody>
</table>

American Cancer Society Guidelines, 2007
Why is MRI superior to mammography in BRCA+?

- BRCA+ breast tumors are:
  - often in younger women with dense breasts – sensitivity of mammography inversely related to breast density
  - with "pushing margins" rather than scirrhous, irregular margins, giving a more "benign" appearance on mammography
  - Less-often associated with DCIS (which often have micro-calcifications that are detected on mammography) – especially true for BRCA1
Distinct features in BRCA1/2 associated breast cancer
BRCA-Related Breast Cancer – distinct features

**BRCA1**
* Breast cancer arises at early age
* Risk of ovarian cancer
* Most (60-70%) are triple negative and basal-like
* Breast cancer reported in very limited number of men

**BRCA2**
* Breast cancer arises at slightly older age
* Risk of ovarian cancer
* Most cancers are ER+ and luminal
* Breast cancer arises in 5-10% of men

*Many similarities, but they are distinct entities and BRCA1 and BRCA2 cancers may not respond identically to treatment*
Predicting BRCA by pathological features

BRCA-Related Breast Cancer – distinct features

• Other features:

<table>
<thead>
<tr>
<th>High grade</th>
<th>Lymphocytic infiltrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mostly invasive ductal carcinoma</td>
<td>TP53 mutations</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>Basal phenotype</td>
</tr>
<tr>
<td>Pushing margins</td>
<td>EGFR expression</td>
</tr>
<tr>
<td>DCIS less common</td>
<td>C-myc amplified</td>
</tr>
</tbody>
</table>

• Bilaterality
Prognosis in BRCA1/2+ Breast Cancer
Is Prognosis different in BRCA1/2 Breast Cancer?

- Local disease
  - Greater incidence of ipsilateral disease
  - Greater incidence of contra-lateral breast cancer – 10yr rate of 26% vs 3% in non-carriers (Pierce et al JCO 2006)
Is Prognosis different in BRCA1/2 Breast Cancer?

- Systemic relapse
  - Most studies report no difference in OS or breast cancer specific survival compared to non-carriers, especially if standard systemic therapy received
    - Rennert et al, NEJM, 2007
    - Goodwin et al, JCO 2012
    - Huzarski et al, JCO, 2013
Goodwin et al, JCO 2012
IMPACT OF A BRCA1/2 MUTATION ON TREATMENT DECISIONS
Impact of a BRCA1/2 mutation on treatment decisions

- **Local management**
  - Lumpectomy vs mastectomy
  - Bilateral mastectomy?
- **Systemic therapy**
  - No EBM to change adjuvant chemotherapy
  - Evidence to support use of DNA cross-linking agents & alkylating agents:
    - Platinum agents, Mitomycin
    - CMF (Cyclophosphamide/MTX/5FU)
- **Reproductive considerations**
- **Ongoing follow-up**
LOCAL THERAPY CONSIDERATIONS
BCS vs Mastectomy

• BCS is a legitimate and safe choice
• Therapeutic radiation is safe:
  - Reduces local ipsilateral recurrence
  - Does not increase contra-lateral disease
• Contralateral mastectomy – some studies suggest that there may be a long term survival benefit
• Decision must be tailored to individual’s needs
Does CRRM improve survival?

Stage 1 & 2 at Dx
Most were <50 at Dx
Metcalfe, BMJ, 2014

Greatest benefit in <40 & low risk/favorable features
Heemskerk-Gerritsen, Int J Cancer, 2015
SYSTEMIC THERAPIES IN BRCA1/2+ BREAST CANCER
Types of DNA damage and repair

**Type of damage:**
- Bulky adducts
- Insertions & deletions
- O6-alkylguanine

**Repair pathway:**
- Base excision repair
- Recombinational repair
- Direct reversal
  - Nucleotide excision repair
  - Mismatch repair

**Repair enzymes:**
- PARPs
- BRCA1/2, RAD51
- DNA-PK
- ATM
- XP, polymerases
- MSH2, MLH1
- AGT
- XRCC1

**Double-strand breaks (DSBs):**
- DNA-PK, HR, NHEJ

**Single-strand breaks (SSBs):**
- PARPs, BRCA1/2, ATM, RAD51
- DNA-PK, HR, NHEJ
Homologous recombination repair pathway:

- important for repairing replication lesions
- depends on the RAD51-family of proteins
- makes use of a homologous DNA sequence.
- BRCA1/2 play a key role in this repair pathway
Chemotherapy
Chemotherapy in BRCA1/2+ Breast Cancer

• Pre-clinical studies suggest increased sensitivity to agents that damage DNA in a way that interferes with DNA replication forks & which subsequently require DNA repair by HR:
  - DNA cross-linking agents (carboplatin, cisplatin, mitomycin)
• Growing body of clinical evidence to support this
Chemotherapy – platinum agents

- Growing number of prospective clinical trials supporting:
  - Incorporation of platinum agents in neo-adjuvant triple-negative BRCA+ breast cancer
  - Phase III study (TNT study) in the metastatic setting favoring caboplatin over docetaxel in triple negative BRCA+ MBC
PARP Inhibitors
The PARP Superfamily

PARP consists of a family of proteins which has multiple members (18) involved in diverse functions including:

- DNA repair
- telomere maintenance
- epigenetic regulation
- centrosomere function
PARP-1 is a key enzyme involved in the repair of single-strand DNA breaks

- A key role in the repair of DNA single-strand breaks
- Uses the base excision repair pathway
- Binds directly to sites of DNA damage
- Once activated, it uses NAD as a substrate and generates large, branched chains of poly(ADP-ribose) polymers on multiple target proteins
- Recruits other DNA repair enzymes
Inhibiting PARP-1 increases double-strand DNA damage.
Inhibiting PARP-1 increases double-strand DNA damage

Inhibition of PARP-1 prevents recruitment of repair factors to repair SSB

DNA SSB

Inhibition of PARP-1 prevents recruitment of repair factors to repair SSB
Inhibiting PARP-1 increases double-strand DNA damage.

Inhibition of PARP-1 prevents recruitment of repair factors to repair SSB.

- Pol β
- PNK 1
- XRCC1
- LigIII

Replication (S-phase)

DNA SSB

DNA DSB
PARP inhibition and tumor-selective synthetic lethality

BRCA1/BRCA2 failure

Chromosomal Instability
Cell Death

PARP inhibition and tumor-selective synthetic lethality

DNA replication fork arrest and collapse

BRCA1/BRCA2 failure

Impaired HR repair

Alternative error prone repair

Normal BRCA1/BRCA2

HR-based repair

Chromosome Stability
Cell Survival

RAD51

Main parachute

Reserve Parachute
Reserve parachute

PARP inhibitor

Main parachute

BRCA mutation

Death of the cancer cell

Reserve Parachute
Increased sensitivity of BRCA1\(^{-/-}\) and BRCA2\(^{-/-}\) cells to PARP inhibition

No difference in sensitivity between heterozygous and wild-type BRCA cells

Targeted inhibition → selective and less toxic therapy

Farmer et al. Nature 2005; 434:917-21
### Phase II, proof-of-concept - Olaparib study, refractory BRCA1/2+ MBC

<table>
<thead>
<tr>
<th>ITT cohort</th>
<th>Olaparib 400 mg bid (n=27)</th>
<th>Olaparib 100 mg bid (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate, n (%)</td>
<td>11 (41)*</td>
<td>6 (22)*</td>
</tr>
<tr>
<td>Complete Response, n (%)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response, n (%)</td>
<td>10 (37)</td>
<td>6 (22)</td>
</tr>
</tbody>
</table>

*An additional 1 patient in the 400 mg cohort and 3 patients in the 100 mg cohort had unconfirmed responses*

Tutt et al, Lancet, 2010
Olaparib Monotherapy in Patients With Advanced Cancer and Germline BRCA1/2 Mutation

- open-label non-comparative trial

- assessing efficacy of olaparib monotherapy (400 mg bid) against BRCA1/2 mutant tumors - "basket study"

- Tumor types included ovarian, breast cancer, prostate cancer and pancreatic cancer

- All patients were heavily pretreated

- 298 patients, responses across all tumor type, ORR was 26.2%

### Olaparib for advanced cancer – study 42

Kaufman et al., JCO 2015

<table>
<thead>
<tr>
<th>Response status, n (%)</th>
<th>Ovarian (n=193)</th>
<th>Breast (n=62)</th>
<th>Pancreas (n=23)</th>
<th>Prostate (n=8)</th>
<th>Other (n=12)</th>
<th>Total (n=298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour response rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>60 (31.1)</td>
<td>5 (21.7)</td>
<td></td>
<td>4 (50.0)</td>
<td>1 (8.3)</td>
<td></td>
<td>78 (26.2)</td>
</tr>
<tr>
<td>CR†</td>
<td>6 (3.1)</td>
<td>0</td>
<td>1 (4.3)</td>
<td>0</td>
<td>0</td>
<td>7 (2.3)</td>
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<tr>
<td>PR†</td>
<td>54 (28)</td>
<td>8 (13)</td>
<td>4 (17)</td>
<td>4 (50)</td>
<td>1 (8.3)</td>
<td>71 (23.8)</td>
</tr>
<tr>
<td>SD ≥8 weeks</td>
<td>78 (40)</td>
<td>29 (47)</td>
<td>8 (35)</td>
<td>2 (25)</td>
<td>7 (58)</td>
<td>124 (42)</td>
</tr>
<tr>
<td>SD</td>
<td>64 (33)</td>
<td>22 (36)</td>
<td>5 (22)</td>
<td>2 (25)</td>
<td>6 (50)</td>
<td>99 (33)</td>
</tr>
<tr>
<td>Unconfirmed PR†</td>
<td>12 (6)</td>
<td>7 (11)</td>
<td>3 (13)</td>
<td>0</td>
<td>1 (8.3)</td>
<td>23 (8)</td>
</tr>
<tr>
<td>PD‡</td>
<td>41 (21)</td>
<td>23 (37)</td>
<td>9 (39)</td>
<td>2 (25)</td>
<td>3 (25)</td>
<td>78 (26)</td>
</tr>
<tr>
<td>RECIST progression</td>
<td>33 (17)</td>
<td>16 (26)</td>
<td>6 (26)</td>
<td>1 (13)</td>
<td>3 (25)</td>
<td>59 (20)</td>
</tr>
<tr>
<td>Early death§</td>
<td>8 (4)</td>
<td>7 (11)</td>
<td>3 (13)</td>
<td>1 (13)</td>
<td>0</td>
<td>19 (6)</td>
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<tr>
<td>Not evaluable</td>
<td>14 (7)</td>
<td>2 (3)</td>
<td>1 (4)</td>
<td>0</td>
<td>1 (8.3)</td>
<td>18 (6)</td>
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<tr>
<td>No follow-up assessments</td>
<td>12 (6)</td>
<td>2 (3)</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>15 (5)</td>
</tr>
<tr>
<td>SD &lt;8 weeks</td>
<td>2 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (8.3)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

80% of ovarian cancer patients - 3+ lines of chemotherapy

Kaufman et al., JCO 2015
Potent PARP inhibitor at MTD as continuous exposure

Physician Choice within SOC options
- Capecitabine
- Vinorelbine
- Eribulin
- Gemcitabine

Primary endpoint PFS

Niraparib – BRAVO Trial EORTC / BIG
Talazoparib – EMBRACA - NCT01945775
Olaparib - OLYMPIAD NCT02000622

OlympiA
OLaparib in Adjuvant
BRCAm breast cancer

Post neoadjuvant gBRCA
HR+, TNBC, Non-PathCR pts

Restricted to Germline Mutation carriers

Post adjuvant gBRCA
HR+,TNBC T2 or N+

Olaparib 300 mg bd
12 month duration

Randomise 1:1
Double blind
N=1500

Placebo
12 month duration

IDFS
Distant DFS; OS

Restricted to Germline Mutation carriers
REPRODUCTIVE ISSUES
Reproductive issues

• Timing of RRSO (risk reducing oophorectomy)
  - For BRCA1 – between 35-40
  - For BRCA2 – by 40
• Fertility preservation
• PGD – pre-implantation genetic diagnosis
• Premature menopause – impact on sexual health, bone health, quality of life
Unique challenges in BRCA1/2 associated Breast Cancer

• Multitude of therapeutic decisions and reproductive decisions
• Knowledge of BRCA1/2 status may arrive at a time of great distress
• Risk reducing measures are often an assault on self-image, “womanhood”
• Far reaching implications for family planning and for the extended family
• Multiple psychosocial issues - support is imperative
• Multi-disciplinary care – is a MUST
Thank you

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