Advanced Ovarian Carcinoma

• What is our standard of care?
  IV carbo/taxol
  IP platinum/taxane (what regimen?)
  IV carbo/taxol/bevacizumab + 12 months of Bev
  IV carbo + dose dense taxol

• Controversy between using PFI and OS as endpoint

• Splitters vs. lumpers
The FA-BRCA Pathway in Ovarian Cancer and Therapeutic Opportunities

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Advanced Ovarian Carcinoma

- GOG158 established **carbo + taxol** as the standard of care vs Cisplatin/taxol, optimal <1 cm

Overall survival **48.7** vs **57.4** months

JCO, 2003
Ozols et al
IP Therapy

• GOG 172 NEJM, 2006 Armstrong et al
• IV Cisplatin (75)/IV taxol vs IP Cis (100), IV taxol D1 and IP taxol D 8
• <1 cm max diam of residual disease
• Only 42% of patients completed 6 cycles
• PFI 18.3 vs 23.8 months (P = 0.05).
• OS 49.7 and 65.6 months, (P = 0.03). 25% reduction in risk of death
Arguments against GOG172

• Was not compared with the standard (IV carbo/taxol)
• Too toxic, few people actually use the published regimen
• Improvement may come from increasing dose density of taxol and not from IP delivery
Dose Dense taxol

- Japanese GOG, Lancet Oncol 2009, Katsumata et al
- Carbo 6 and taxol weekly at 80mg/m²

55% of cases were suboptimal, HR .75 in favor of experimental arm, Median survival not yet reached at 42 months, but at 3 tears was 72% vs 65%

First dose density study in ovarian cancer with such positive results, Could it be influenced by genotypes and phenotypes of ovarian cancer in Japanese population
GOG218

- 3 armed trial, Carbo/taxol IV vs Carbo/taxol/Bev, Vs. carbo/taxol/Bev + 12 months of Bev, NEJM, 2011, Burger et al
- Primary endpoint was PFI, not overall survival
- The median progression-free survival was 10.3 months in the control group, 11.2 in the bevacizumab-initiation group, and 14.1 in the bevacizumab-throughout group.
Issues with GOG218

• No difference in OS,
  — though this was not intent of trial, after unblinding crossover occurred

• EXPENSIVE!!!

• Relative small difference in PFI for increase in toxicity, treatment length and cost
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I have not even mentioned Neoadjuvant chemo!
PFI vs Overall Survival

• Controversy between using PFI and OS as endpoint
• GOG used PFI to shorten trials and put together optimal/suboptimal to increase speed of accrual, data in Ovarian cancer that PFI correlated with OS
• FDA does not want to approve drugs based on PFI and not survival
• As we have lengthened OS without changing overall mortality is it realistic to run longer and longer trials to test impact on OS
• Many women now get 6-10 treatment regimens during course of disease, will we lose the impact on OS as women survive to get newer secondary treatments
Next GOG Phase III trial

Patients with stage III/IV ovarian cancer

Carboplatin/paclitaxel + Placebo

Carboplatin/paclitaxel + PARP inhibitor

Carboplatin/paclitaxel + Placebo

Carboplatin/paclitaxel + PARP inhibitor

Placebo

Placebo

PARP inhibitor

PARP inhibitor
PARP inhibitors and synthetic lethality

DNA damage

HR:
- BRCA1/2
- Rad51
- FA proteins

Error-free repair
- Cell survival

PARP1

Error-prone repair
- Genomic instability
- Chromosomal rearrangements
- Cell death

NHEJ:
- DNA-PK

A Patel et al., PNAS 108:3406, 2011
PARP inhibitors and synthetic lethality

Approximate 40% response rate in recurrent ovarian and breast carcinomas associated with BRCA1/2 mutations to olaparib

A Patel et al., PNAS 108:3406, 2011
Cancer Treatment Paradigm

Tumors → Genes → Targets → Drugs
Cancer Treatment Paradigm

Tumors → Genes → Targets → Drugs
Ovarian Carcinoma

• *BRCA1* and *BRCA2* account for the majority of hereditary ovarian carcinoma

• *BRCA1/2* play key roles in the Fanconi anemia (FA)-BRCA pathway
  – repairs double-strand DNA breaks through homologous recombination (HR)

• Sensitivity to platinum and PARP inhibitors

• Many sporadic serous ovarian cancer and TNBC are thought to have a BRCA deficient phenotype
Hereditary Ovarian Cancer

• Previous studies have shown that 13-15% of ovarian cancer patients in North America carry germline mutations in BRCA1 or BRCA2
  – These two genes thought to account for nearly all hereditary cases
• Second contributor were genes associated with Lynch syndrome
  - fraction of cases not known
• Contribution of other tumor suppressor genes was uncertain
• Identifying hereditary cases is important for
  – Targeted cancer prevention in unaffected women
  – Use of PARP inhibitors or other targeted therapies in affected women.
Causes of Hereditary Susceptibility to Ovarian Cancer

- Sporadic (~90%)
- Hereditary (~10%)

Changes in:
- Sporadic (~85%)
- Hereditary (~15%)
Causes of Hereditary Susceptibility to Ovarian Cancer - 2010

- Sporadic (~85%)
- Hereditary (~15%)
  - BRCA1 (~60%)
  - BRCA2 (~33%)
  - HNPCC (~2%)
  - Other single genes (~5%)
Fanconi Anemia (FA)-BRCA Pathway

- Repairs double strand DNA breaks
- Germline mutations increase risk of breast cancer
- Data from us and others implicate in ovarian cancer risk
New Kids on the Block

• *RAD51C* identified in breast and ovarian cancer families (Meindl et al, Nat Genet, 2010), 6/480 br/ov (1.3%), 0/620 br only families
New Kids on the Block

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- **RAD51D** identified in breast and ovarian cancer families (Loveday, et al, Nat Genet 2011), increased risk of ov ca (6.3x) but not sign increase risk of breast cancer, 8/911 br/ov (0.9%) and 0/737 br only families
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- *BRIP1* Icelandic founder frameshift mutation, 8X RR of ovarian cancer (Rafnar et al, Nat Genet, 2011), second rare Spanish frameshift mutation markedly increased risk of ov (25x) and br cancer
New Kids on the Block

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Mutations are rare, even amongst high risk families
Targeted Capture and Next Gen Sequencing: BROCA

- Mary-Claire King Ph.D.
- Named after Paul Broca - the 19th century neurosurgeon and anatomist who described inherited breast and ovarian cancer
Next Gen sequencing

• Targeted capture and massively parallel sequencing allows identification of mutations of all classes, with testing of many genes simultaneously at low cost
• Flexible- can choose targets
• High read depth allows greater sensitivity
• Including introns and high coverage allows detection CNVs (no need for a separate test to detect rearrangements)
Massively Parallel Sequencing

1. Sonicate (3μg DNA)
2. Paired-end library (200bp)
3. Hybridize to biotinylated capture bait oligos (21 gene regions)
4. Bar Code 96 samples
5. Purify with streptavidin beads
6. Detect variants (MAQ and BWA)
7. Compare to dbSNP and mutation specific databases
8. 2 x 76bp reads

Massive Parallel Sequencing

Detect variants (MAQ and BWA)

Compare to dbSNP and mutation specific databases
BROCA

• 360 women with primary ovarian, peritoneal, or tubal carcinoma
  – Enrolled at diagnosis
  – Not selected for age at onset or family history

• Genomic DNA screened for mutations in 21 tumor suppressor genes
Targeted capture and sequencing: BROCA

Panel of 21 tumor suppressor genes

<table>
<thead>
<tr>
<th>High risk</th>
<th>FA BRCA pathway</th>
<th>Rare syndromes</th>
<th>Lynch syndrome</th>
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<tbody>
<tr>
<td>BRCA1</td>
<td>PALB2</td>
<td>TP53</td>
<td>MSH2</td>
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<td>BRCA2</td>
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<td>CDH1</td>
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<td>STK11</td>
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<tr>
<td></td>
<td>RAD51C</td>
<td>MUTYH</td>
<td>PMS1</td>
</tr>
</tbody>
</table>

Normalized depth of coverage across the 21 genes
Results

- 85 germline loss-of-function mutations in 12 genes (24% subjects)
  - 18% with mutation in BRCA1 or BRCA2
  - 6% in other genes

PNAS, Walsh et al 2011
Targeted capture and sequencing: BROCA

Panel of 21 tumor suppressor genes

High risk

<table>
<thead>
<tr>
<th>BRCA1</th>
<th>BRCA2</th>
<th>FA-BRCA</th>
<th>Rare syndromes</th>
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<td>TP53</td>
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<tr>
<td>BRIP1</td>
<td>ATM</td>
<td>MRE11A</td>
<td>PTEN</td>
<td>MSH1</td>
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<tr>
<td>RAD50</td>
<td>BARD1</td>
<td></td>
<td>CDH1</td>
<td>MSH6</td>
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<tr>
<td>RAD51C</td>
<td></td>
<td></td>
<td>STK11</td>
<td>PMS2</td>
</tr>
</tbody>
</table>

**RAD51D**

Normalized depth of coverage across the 21 genes

1p 22q
Causes of Hereditary Susceptibility to Ovarian Cancer-2012

- Sporadic (~10%)
- Hereditary (~15%)
- Hereditary (~25%)
Causes of Hereditary Susceptibility to Ovarian Cancer

Sporadic

Hereditary (~25%)

BRCA1 (~47%)

BRCA2 (~23%)

Other single genes (~29%)

HNPCC (<1%)
BRCA-FA genes only

- Targeted capture and massively parallel genomic sequencing 21 genes
- Sanger sequencing reveals an addition 1% of cases with RAD51D mutations

<table>
<thead>
<tr>
<th>Cases</th>
<th>BRCA1/2 mutation</th>
<th>FA-BRCA gene mutation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=360</td>
<td>63 (17.5%)</td>
<td>21 (5.8%)</td>
<td>84 (23.3%)</td>
</tr>
</tbody>
</table>

Walsh, et al. PNAS (November, 2011)
BRCA deficient phenotype

• Long been suggested that there are sporadic ovarian cancers with deficiencies in FA-BRCA pathway (BRCAness)
• These cases could also be sensitive to platinum and to PARP inhibitors
• Could be mediated by small mutations, gene rearrangements or epigenetic alterations
• Platinum sensitive recurrent ovarian cancer sp PR/CR to platinum regimen
• Randomized Phase II, rec’d placebo or maintenance olaparib
• 22% had BRCA1/2 mutations, 63% not tested
Olaparib Study 19

- No difference in overall survival (data not mature)
- AZ has suspended clinical development of the drug.
Hypothesis

• The presence of germline or somatic mutations in FA-BRCA pathway genes predicts primary platinum sensitivity
Study Design

- N= 297 subjects
  - 219 of the 360 women previously tested for germline mutations with BROCA
  - 78 cases not previously tested with BROCA
- **Neoplastic** DNA tested for mutations in 30 tumor suppressor genes using BROCA, only 13 are from the FA-BRCA pathway
- Mutations were verified by Sanger Sequencing
Overall Mutation Rate

- 22% germline mutations
- 15% somatic mutations
Germline Mutations

• 22% of cases
Somatic Mutations

- 15% of cases

- BRCA1: 37%
- BRCA2: 8%
- CHEK2: 10%
- PTEN: 33%
- BRIP1
- MRE11A
- RAD50
- RAD51C
- ATM
Primary Platinum Sensitivity

Germline mutations

Platinum sensitive

Refractory/resistant
Primary Platinum Sensitivity

- Platinum sensitive
- Refractory/resistant

Somatic mutations

Germline mutations
Primary Platinum Sensitivity

- No mutations
- Germline mutations
- Somatic mutations

Platinum sensitive

- Refractory/resistant
Primary Platinum Sensitivity

- Germline mutations
- Somatic mutations
- No mutations

P < 0.01
Primary Platinum Sensitivity

- Median survival by mutation status:
  Germline 66 months, somatic 54 months, wildtype 49 months
Conclusions

• At least 35% of ovarian/FT/peritoneal carcinomas are associated with germline or somatic mutations in the 13 FA-BRCA genes in our panel

• Having either a germline or somatic mutation in a FA-BRCA gene predicts primary platinum sensitivity

• New version of BROCA includes 40 HR genes
Next GOG Phase III trial

Patients with stage III/IV ovarian cancer

Embedded translational research component:
- Correlate the presence of germline mutations with response, survival, and toxicity
- Identify somatic mutations for DNA repair genes, and correlate to therapeutic outcomes
Challenges with PARPi development

• Niche market, may not be profitable
• Not all PARPi’s are equivalent
• Olaparib was the furthest along in development, AstraZeneca has suspended clinical development presently
  – Unable to formulate tablet easily
  – No difference in phase III study comparing Doxil vs Olaparib in plat resistant (<12 months) BRCA1/2 carriers (JCO, Kaye et al 2012)
**PARPi’s in development**

- **Olaparib** AstraZeneca, ORAL, clear efficacy as single agent, have halted clinical development.
- **Veliparib** (ABT-888)-ORAL, CTEP agent, 10 fold less potent than olaparib in vitro, monotherapy trial in mutation carriers about to open in GOG, in phase I and II trials.
- **Iniparib**: IV may not function as PARP inhibitor at clinical doses, encouraging phase II data led to Phase III study of iniparib in combo with gem/carbo in TNBC- that trial was negative.
- **Rucaparib**-ORAL, Licensed by Pfizer to Clovis, they are small public company dedicated to developing targeted agents in conjunction with companion diagnostics, in phase I/II trials, appears equipotent to olaparib in vitro.
- **MK-82770** ORAL, Merck, phase I and II studies, probably will off-load.
Genetic testing for Ovarian Cancer Risk

• Will need to incorporate a multigene panel to detect most hereditary cases
• These multigene panels using Next Gen sequencing approaches are already being offered clinically for genetic testing
• 1/3 of women with germline mutations have no family history of disease, and likelihood of case being hereditary does not fall with age until diagnosed after age 70
• The US Supreme Court recently asked the appeals court to reconsider their decision on the Myriad patent case
• Genetic testing for cancer susceptibility is likely to change dramatically in the near future- get to know a good genetic counselor
NEANDERTHAL MAN

RODNEY MICKLETHWAITE

RODNEYS FAMILY TREE WAS A LOT SHORTER THAN MOST
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