Ovarian Cancer: Where we are and where we are going…

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Gayle’s Story
Gayle’s Story

- Gayle G., 47 yo, married, mother of two (21 yo daughter, 25 yo son)
- Roanoke Rapids, NC, real estate agent
- 4 month history of constipation and abdominal bloating – had undergone many treatments for this by her primary care physician
- Referred from Surgical Oncology Clinic for concern of ovarian cancer.
- Evidence of an advanced ovarian cancer on imaging.
- Up to date on mammograms, colonoscopies and pelvic exams.
Gayle’s Story

- Underwent surgery followed by 6 cycles of chemotherapy.
- Complete response to treatment.
- 9 years later – no recurrences
- Relay for Life, welcomed many grandchildren into the world (4 years old, 2 years old and 8 months old.)
Ovarian Cancer

- Worldwide: 204K cases, 125K deaths
- US: 22K cases, 14K deaths
- 75% of patients present with advanced disease, Stage III/IV
- 5 year survival is 30-50%
- 1/10 as common as breast cancer but 3X more lethal
## Cancer statistics, 2015

### Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>220,800</td>
<td>Breast</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>115,610</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>69,090</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>56,320</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>42,670</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>39,850</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>38,270</td>
<td>Melanoma of the skin</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>32,670</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Leukemia</td>
<td>30,900</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>25,510</td>
<td>Kidney &amp; renal pelvis</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>848,200</strong></td>
<td><strong>All Sites</strong></td>
</tr>
</tbody>
</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>86,380</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>Prostate</td>
<td>27,540</td>
<td>Breast</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>26,100</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>Pancreas</td>
<td>20,710</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>17,030</td>
<td>Ovary</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,210</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,600</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>11,510</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,480</td>
<td>Liver &amp; intrahepatic bile duct</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>9,070</td>
<td>Brain &amp; other nervous system</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>312,150</strong></td>
<td><strong>All Sites</strong></td>
</tr>
</tbody>
</table>

Ovarian Cancer Facts

- Mean age = 63 years
- Average risk 1 in 70 women = 1.8%
- If 1st degree relative has ovarian cancer, the risk increases to 4-5%.
OVARIAN CANCER RISK FACTORS

- Less ovulation—less risk
- Nulliparous or low parity
- Pregnancy reduces by 25-50%
- Breast feeding reduces by 20%
- Oral contraceptives protective (reduced risk 50% over 10 + yrs)
- Tubal ligation and hysterectomy reduces by 15% (ovaries left in place)
- Associated with overweight/obesity
- Associated with genetic syndromes
  » BRCA1 and 2 high risk mutations
## Silent Killer??

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>% OF TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>50.8</td>
</tr>
<tr>
<td>Abdominal swelling</td>
<td>49.5</td>
</tr>
<tr>
<td>G.I. Complaints</td>
<td>21.6</td>
</tr>
<tr>
<td>Weight loss</td>
<td>17.5</td>
</tr>
<tr>
<td>Abnormal bleeding</td>
<td>17.1</td>
</tr>
<tr>
<td>Urinary Symptoms</td>
<td>16.4</td>
</tr>
<tr>
<td>Pelvic pressure</td>
<td>5.0</td>
</tr>
<tr>
<td>Backache</td>
<td>4.9</td>
</tr>
<tr>
<td>Mass felt by patient</td>
<td>2.8</td>
</tr>
<tr>
<td>None</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Gynecologic Oncology---Ed. Coppleson
OVARIAN CANCER SCREENING

• There are NO available techniques currently suitable for routine screening for ovarian cancer.

• CA-125
  » Only increased in 50% of early ovarian cancers.
  » Can be increased for reasons other than ovarian cancer.

• Pelvic Ultrasound
  » Can tell if it isn’t cancer.
  » Cannot tell if it is cancer.

• CA-125 + pelvic ultrasound – so far increased harm but no improvement in detection or survival rates
Late diagnosis results in poor survival

If diagnosed at the localised stage, the 5-year survival rate is 93%. However, only about 15% of all cases are diagnosed at this stage.

Localised
Confined to primary site
15% at diagnosis

Regional
Spread to regional lymph nodes
17% at diagnosis

Distant
Cancer has metastasised
62% at diagnosis

Unknown
Unstaged
7% at diagnosis

• The best we have for “screening” – pay attention to these symptoms.
  » Bloating
  » Pelvic or abdominal pain
  » Difficulty eating or feeling full quickly
  » Urinary symptoms (urgency or frequency)
Management of Ovarian Cancer

• Surgery – hysterectomy, removal of ovaries and fallopian tubes, debulking

• Chemotherapy

• Radiation – only used in special cases
Chemotherapy was very toxic
Nitrogen mustard
Alkylation agents (cytoxan, melphalan)
Poor response rates
1990’s – 2000’s
Taxanes!
Carboplatin!
Taxanes + Carboplatin:

- Well tolerated
- Response rate - 75%
- These are not cure rates for women with advanced stage disease – 75% of women will recur.
- Improvements in treatment are needed!
Metformin

- Anti-diabetic medicine from the biguanide class.
- Metformin use may lower cancer risk and reduce cancer deaths among diabetic patients.
- >80 clinical trials in regards to metformin and cancer listed on www.clinicaltrials.gov.
- Translational/pre-operative window trials, treatment trials, prevention trials and survivorship trials.
- 4 trials in ovarian cancer.
## Metformin and Ovarian Cancer Outcomes

<table>
<thead>
<tr>
<th>Author-Year</th>
<th>Study Type</th>
<th>Tumor Type</th>
<th>No. Patients: Database-yrs collected</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romero IL <em>et. al.</em>, Obstetrics and Gynecology, 119: 61-7 (2012).</td>
<td>Retrospective cohort</td>
<td>Ovarian</td>
<td>341 (44 diabetic): Single institution database 1992-2010</td>
<td>PFS was improved in patients with type 2 diabetes on metformin (51%) vs non-diabetics (23%) vs diabetics not on metformin (8%), p=0.03. OS also improved 63, 37, 23% respectively, p=0.03.</td>
</tr>
<tr>
<td>Currie CJ <em>et. al.</em>, Diabetes Care, 35:299-304 (2012)</td>
<td>Retrospective cohort</td>
<td>Ovarian and endometrial</td>
<td>112,408 (8392 diabetic): &gt;350 primary care centers in the U.K. 1990-2009</td>
<td>Diabetics taking metformin at the time of diagnosis, had half the risk of dying when compared to non-metformin users (HR: 0.48, 95% CI: 0.28–0.81)</td>
</tr>
</tbody>
</table>
Metformin’s Anti-Tumorigenic Effects

- **Indirect** – improvement in insulin resistance, decrease in circulating insulin and glucose
- **Direct** – AMPK activation, leading to inhibition of the mTOR pathway
Metformin and Ovarian Cancer Cell Lines

- Inhibits ovarian cancer cell growth.
- Induces ovarian cancer cell death
- Inhibits targets of the mTOR pathway.
- Behaves synergistically with paclitaxel and platinums.
• Heat map representation of 131 genes found to be significantly up- or down-regulated in the ovarian tumors from the obese versus non-obese KpB mice (FDR<0.1).
  - lipocalin
  - fatty acid amide hydrolase
  - ectonucleoside triphosphate diphosphohydrolase
  - fatty acid 2-hydroxylase
  - glycerol-3-phosphate acyltransferase
  - protein phosphatase
  - protein kinase C
  - AMP deaminase 3

• Obesity increased tumor size in KpB mice.
• Obese mice weighed significantly greater than non-obese mice (31 gm versus 51 gm, p=0.003).
• The ovarian tumors were tripled in size in the obese mice as compared to non-obese mice (mean size of 3.7 cm² versus 1.2 cm², p=0.0065).
Comparison of metabolic differences between the ovarian tumors from obese and non-obese KpB mice. *p≤0.05, #0.05<p<0.1

<table>
<thead>
<tr>
<th>Sub-Pathway</th>
<th>Biochemical Name</th>
<th>Obese/Non-Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycolysis, Gluconeogenesis and Pyruvate Metabolism</td>
<td>Glucose</td>
<td>2.76*</td>
</tr>
<tr>
<td></td>
<td>Fructose-6-phosphate</td>
<td>0.52#</td>
</tr>
<tr>
<td></td>
<td>Isobar: F1, 6BP, G1, 6BP, myo-INS BPs</td>
<td>0.45#</td>
</tr>
<tr>
<td></td>
<td>Pyruvate</td>
<td>0.48*</td>
</tr>
<tr>
<td>TCA cycle</td>
<td>Succinate</td>
<td>4.04#</td>
</tr>
<tr>
<td></td>
<td>Fumarate</td>
<td>0.62*</td>
</tr>
<tr>
<td></td>
<td>Malate</td>
<td>0.71#</td>
</tr>
</tbody>
</table>
Metformin inhibited ovarian tumor weight and volume in obese and non-obese KpB mice. In obese mice, metformin decreased tumor weight/volume by 60% compared to obese controls. Tumor weight/volume only decreased by 32% in non-obese mice compared to non-obese controls. A comparison of the anti-tumorigenic effects of metformin on ovarian tumors from non-obese and obese mice demonstrated that metformin was more efficacious in obese mice (p=0.003), suggesting that metformin may be more beneficial in the setting of obesity.
• Decreased cell proliferation (Ki-67).
• Induced cell death (caspase 3).
• Inhibited the mTOR pathway (AMPK and S6).
Time to move to a clinical trial.......
Metformin and Ovarian Cancer Clinical Trials

• A Phase II, Open-Label, Non-Randomized, Pilot Study of Paclitaxel, Carboplatin and Oral Metformin for Patients Newly Diagnosed with Stage II-IV Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Carcinoma
  » Debulking surgery + paclitaxel/carboplatin/metformin
  » Supported by the Nancy Yeary Womens Cancer Research Foundation & Hoag Hospital Cancer Center
  » 16/30 patients have been enrolled
  » Serum, urine and tissue being collected
<table>
<thead>
<tr>
<th>Center</th>
<th>Title</th>
<th>Trial type</th>
<th>Tumor types</th>
<th>Study interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Chicago NCT02122185</td>
<td>Metformin Hydrochloride and Combination Chemotherapy in Treating Patients With Stage III-IV Ovarian, Fallopian Tube, or Primary Peritoneal Cancer</td>
<td>Randomized, placebo controlled, phase II trial</td>
<td>Ovarian /Fallopian tube/Primary peritoneal</td>
<td>Patients receive metformin BID or placebo BID in combination with standard chemotherapy for 6 courses.</td>
</tr>
</tbody>
</table>
| University of Michigan Cancer Center NCT01579812 | A Phase II Evaluation of Metformin, Targeting Cancer Stem Cells for the Prevention of Relapse in Patients With Stage IIC/III/IV Ovarian, Fallopian Tube, and Primary Peritoneal Cancer | Open label, efficacy trial         | Ovarian/ Fallopian tube/ Primary Peritoneal | (1) Patients receiving primary surgical debulking followed by standard chemotherapy will initiate metformin prior to primary surgery.  
(2) Patients treated with neoadjuvant chemotherapy will be initiated on metformin prior to the initiation of chemotherapy. |
| Fox Chase Cancer Center NCT02050009   | The Use and Safety of Metformin, Carboplatin and Paclitaxel in Non-Diabetic Patients With Recurrent, Platinum Sensitive Ovarian Cancer and the Feasibility of Using a Core Biopsy for RNA-Seq | Open label, efficacy trial | Ovarian                              | Patients receive metformin BID on days 1-21, paclitaxel IV over 3 hours on day 1, and carboplatin IV over 30 minutes on day 1. |
Advantages of Metformin Therapy

- Low cost
- Oral route of administration
- Low toxicity
Conclusions

• Taxol and carboplatin have dramatically improved outcomes for ovarian cancer.
• Most women with ovarian cancer will recur.
• More treatment options are needed.
• The pre-clinical, epidemiologic and clinical data supporting the use of metformin in the treatment of cancers is building.
• Multiple clinical trials are in progress – including here in Newport Beach, CA.
• **My Laboratory (past and present):** Chunxiao Zhou (Lab Manager), Emily Ko, Leigh Cantrell, Rabbie Hanna, Albert Mendivil, Kevin Schuler, Anuj Suri, Josh Kilgore, Amanda Jackson, Kim Malloy, Yi Sun, Yan Zhong, Haifeng Qiu, Xiaoyun Han, Lingquin Yuan, Hallum Dickens, Tim Gilliam, Monica Schiointuch, Jessica Stine, Kemi Doll, Dario Roque, Weiya Wysham

• **Collaborators:** Paola Gehrig, MD, Liza Makowski, PhD, Dhiren Thakker, PhD, Siobhan O’Connor, Brante Sampey, PhD, Megan Difurio, MD, Brooke Rambally, MD, David Kaufman, MD, PhD, Lisa Abaid, MD

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Thank you!
Questions??

Nancy Yeary
Women’s Cancer Research Foundation

SHE ROCKS
RESEARCH OVARIAN CANCER KNOWLEDGE SUPPORT