Granulosa Cell Tumors and Immunotherapy for Ovarian Cancer

Kunle Odunsi, M.D., Ph.D.$^{1,2,3}$
Cancer Center Deputy Director

Departments of Gynecologic Oncology$^1$, Immunology$^2$, Center for Immunotherapy$^3$
Roswell Park Cancer Institute
Buffalo, NY
Adoptive T Cell Therapy

ACT, scientists teach the T cells to give them a fighting chance. Studded cells tell them “testing drugs.”

To better understand the full potential of this therapy, researchers are still learning to control the cells’ power to ensure they can vanquish cancer without damaging normal tissues—a task complicated by the fact that cancer antigen targets are also found on normal cells. Another problem is that it’s not yet clear how to turn ACT into a viable treatment option, a hurdle that must be overcome before the drug can reach patients. The number of patients varies much more than the number of patients.

But there are also scientific and logistical challenges to expanding the use of this therapy. These challenges involve the complexity of the immune system and the need for precise targeting. A better understanding of how the immune system works could help to address these challenges. One solution is to use CAR T cells to target specific tumor cells. This approach could potentially be used to treat a wide range of cancers, as CAR T cells are engineered to recognize and destroy tumor cells.
Types of Ovarian Cancer

25,000 new cases of ovarian cancer in the US each year
more than 14,000 deaths

1,500-2,000 new cases of Granulosa-Thecal tumors each year
What are granulosa cells?
Granulosa Cell Tumors: Fast Facts

- Include tumors composed of granulosa cells, theca cells, and fibroblasts in varying degrees and combinations.

- GCTs account for approximately 2% of all ovarian tumors:
  - Adult (95%)
  - Juvenile (5%) types based on histologic findings. Both subtypes commonly produce estrogen.

- **Adult GCTs** (AGCTs) usually occur in postmenopausal women and have late recurrences.

- **Juvenile GCTs** (JGCTs) develop in individuals <30 yrs old and often recur within the first 3 years.
Why and how?

• No clear cause identified

• Genetic studies: point mutation (C402G) in *FOXL2*
  – 100% of 4 adult GCTs
  – Confirmed in an additional **86 of 89 adult GCTs**
  – *And 1 in 10 juvenile-type GCTs*
  – Not found in any epithelial ovarian tumors

This the possibility of identifying novel targeted therapies
Additional Facts

• AGCTs and JGCTs have very good cure rates due to early stage of disease at diagnosis.
  – >90% diagnosed before spread occurs outside ovary.
  – AGCTs usually are seen in postmenopausal women, with a median age at diagnosis of 52 yrs

• 5-year survival rates usually 90-95% for stage I tumors
  – 25-50% for patients presenting with advanced-stage disease

• AGCTs have a propensity for late recurrence
  – some occur as many as 37 yrs after diagnosis
  – mean survival after the diagnosis of recurrence is 5 yrs

• Approximately 20% of patients diagnosed with GCTs die of their disease over the course of their lifetime.
Signs and Symptoms

• Manifestations of excessive estrogen
  – ~70% of these tumors are hormonally active

• Reports of increasing abdominal girth and abdominal discomfort
  – Acute abdominal or pelvic pain may be observed
  – in combination with nausea, vomiting, dizziness, shoulder pain

• Prepubertal girls: usually present with precocious pseudopuberty (70-80%) and have secondary sex characteristics at a very early age.

• Postmenopausal women: abnormal uterine bleeding, endometrial hyperplasia and/or endometrial carcinoma
Laboratory studies

• Prepubertal or <30 yrs old
  – bhCG, alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), CA125.

• Reproductive-aged women >30 yrs old
  – CA125, inhibin, Hormones, if suggested based on clinical findings.

• Postmenopausal women
  – CA125, hormones

• Others
  – Inhibin A & B; AMH or MIS

• Imaging studies
• Histology (Microscopy)
Microfollicular pattern; Call-Exner bodies and nuclear grooves
Treatment

• Surgery; stage is most important prognostic factor

• In younger patients who desire future fertility
  – unilateral salpingo-oophorectomy is usually sufficient

• Current chemotherapy regimens usually multidrug
  – most frequent combination therapy given currently is bleomycin, etoposide, and cisplatin (BEP)
  – carboplatin and paclitaxel for patients with advanced or recurrent chemotherapy-naive sex cord stromal tumors

Challenge: recurrent, metastatic disease
But, little research on novel therapies
Why harness the immune system against cancer?

Vaccination against infectious diseases has proven cheap, safe and extremely successful in preventing illness and death.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Baseline 20th century annual morbidity</th>
<th>1998 provisional morbidity</th>
<th>% decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>48,164</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>175,885</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Pertussis</td>
<td>147,271</td>
<td>6,279</td>
<td>95.7</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1,314</td>
<td>34</td>
<td>97.4</td>
</tr>
<tr>
<td>Poliomyelitis (paralytic)</td>
<td>16,316</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Measles</td>
<td>503,282</td>
<td>89</td>
<td>100</td>
</tr>
<tr>
<td>Mumps</td>
<td>152,209</td>
<td>606</td>
<td>99.6</td>
</tr>
<tr>
<td>Rubella</td>
<td>47,745</td>
<td>345</td>
<td>99.3</td>
</tr>
<tr>
<td>Congenital rubella syndrome</td>
<td>823</td>
<td>5</td>
<td>99.4</td>
</tr>
<tr>
<td>Haemophilus influenzae type b</td>
<td>20,000</td>
<td>54</td>
<td>99.7</td>
</tr>
</tbody>
</table>
Major advances in the last 10 years

• Your immune system protects you against cancer.
Significance of anti-tumor immunity in ovarian cancer

Sato et al, PNAS, 2005, 102:18538

Intraepithelial CD8+ TIL

- lowest tertile
- all others

Log Rank test

P=0.009

Median survival: 55 vs 26 months

Hazard ratio: 0.33 (p = 0.0003)
Major advances in the last 10 years

- Your immune system protects you against cancer.
- Cancer vaccines
- Immune checkpoints
  - CTLA4 and PD-1/PD-L1 pathways

- Adoptive cellular therapy
How cancer vaccines prolong survival

Chemotherapy/radiation therapy

Immunotherapy

Amount of tumor

Time

Time
Which antigens should we target with cancer vaccines?

- A protein that is expressed in cancer but NOT in other normal cells of the body.
- Best examples are CANCER TESTIS ANTIGENS, e.g. NY-ESO-1.

NY-ESO-1 expression

Testis

Ovarian Cancer
How are lymphocytes “instructed” to attack?

Antigen Presentation

- e.g. NY-ESO-1

Dendritic cell

“eats” bacteria or NY-ESO-1

The Dendritic Cell presents the antigen (NY-ESO-1) to a T cell

Parts of the bacteria or NY-ESO-1 (antigen) goes to the surface of the DC

The T cell is activated

T cell (happy)

Destroy NY-ESO-1+ve targets

The Battle Begins
Types of Cancer Immunotherapy

- Antibodies
- Vaccines
- Immune Checkpoint Inhibitors / Modulators
  - CTLA-4, PD-1/PD-L1 Inhibitors
- Cellular therapies
  - Adoptive T cell therapy
Cancer Vaccines

- Fragments of tumor antigen (peptides) + adjuvant (NY-ESO-1)
- Full length antigen protein + adjuvant
- Viruses engineered to express cancer antigen
- Personalized dendritic cells
  - loaded with antigen or tumor lysate
- Combined with other immune modulators
Phase II Trial: rVaccinia/rFowlpox-NY-ESO-1 vaccination

Overall Survival by Immune Response Category

Median 53 mths
Median 48 months
Median 14 months

GOG 182: OS 40mths
An innovative immunotherapy that specifically targets and kills cancer cells
Aseptic Manufacturing
Controlled Manufacturing Environment
- temperature
- humidity
- pressure
- particulates
- gases
Continuous real-time monitoring
Challenges Confronting Development of Cancer Immunotherapy

The tumor environment is an immunological battle ground: Good vs. Bad
Conclusions

• Cancer immunotherapy offers the possibility for long-term cancer remission.
• Cancer immunotherapy may not cause the same side effects as chemotherapy and radiation.
• Vaccines, Immune checkpoint, adoptive T cell therapies (ACT).
• Combination strategies.
  – Vaccines ± immune checkpoint; vaccines ± ACT
  – Adoptive T cell therapy ± immune checkpoint
  – Vaccines ± chemotherapy.
• We can apply these same strategies to GCT: collaborations/funding will be required.
• Choosing the right clinical trial.