Advanced/Recurrent Endometrial Cancer:
First-line Treatment should be Chemotherapy
PRO

Gini Fleming
GCIG June 1, 2017
EC First-Line Chemotherapy

• Currently carboplatin/paclitaxel
  – Provides tumor shrinkage with palliation of symptoms for the majority of patients
  – 22% CR (paclitaxel/doxorubicin/cisplatin)
  – Cost moderate
  – Prolonged DFS in a small number
GOG 177

Endometrial Cancer
Stage III/IV/Recurrent
Measurable Dz
No prior Chemo

Randomize

Cisplatin 50 mg/m²
Doxorubicin 45 mg/m²
Paclitaxel 160 mg/m² + GCSF (TAP)

Cisplatin 50 mg/m²
Doxorubicin 60 mg/m² (AP)

Accrual complete
Aug 2000
GOG 177

- N=273
- Up to 7 cycles (no maintenance)
- For TAP
  - RR 57%
  - CR 22%
  - PFS 8.3 months
  - OS 15.3 months
- Terminated in 2009 (no more survival data)

JCO 22:2159,2004
GOG 177 OS

GOG 0177
Overall Survival

Treatment

AP

TAP

Events
Total
121 129
112 134

Proportion Alive

0.0
0.2
0.4
0.6
0.8
1.0

Months on Study

0 12 24 36 48 60 72

AP

129 66 26 19 12 10 9

TAP

134 80 49 32 26 21 21
GOG 177 PFS

GOG 0177
Progression-Free Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP</td>
<td>123</td>
<td>129</td>
</tr>
<tr>
<td>TAP</td>
<td>116</td>
<td>134</td>
</tr>
</tbody>
</table>

Proportion Alive, Progression-Free

Months on Study

AP 129 20 7 7 7 6
TAP 134 43 22 18 15 15
Progression-Free Survival
By Cell Type

Group
- Clear Cell
- Serous
- All Others

Alive,PF Failed Total
1 7 8
4 41 45
24 186 210

Proportion Surviving Progression-Free

Months on Study

GOG 177
# Endometrial Cancer Histology and Chemotherapy Outcomes

GOG 107, 139, 163, 177

<table>
<thead>
<tr>
<th>Histology</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
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<tbody>
<tr>
<td>Endometrioid (n=622)</td>
<td>44%</td>
<td>6.4 mos</td>
<td>13 mos</td>
</tr>
<tr>
<td>Serous (n=217)</td>
<td>44%</td>
<td>6.3 mos</td>
<td>11 mos</td>
</tr>
<tr>
<td>Mixed (n=102)</td>
<td>37%</td>
<td>5.7 mos</td>
<td>15 mos</td>
</tr>
<tr>
<td>Clear Cell (n=44))</td>
<td>32%</td>
<td>3.2 mos</td>
<td>8 mos</td>
</tr>
</tbody>
</table>

McKmeekin S, Gyn Oncol, 2009
GOG 209

Survival
By Randomized Treatment

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Alive</th>
<th>Dead</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP</td>
<td>299</td>
<td>343</td>
<td>642</td>
</tr>
<tr>
<td>TC</td>
<td>295</td>
<td>368</td>
<td>663</td>
</tr>
</tbody>
</table>

Figure 1
Endometrial Cancer

• Use of adjuvant chemotherapy has increased in past decades
  – How does receipt of prior adjuvant chemotherapy (usually carboplatin/paclitaxel) affect subsequent benefit from carboplatin/paclitaxel?
  – Using “platinum sensitivity” for endometrial cancer?
SGSG-012/GOTIC-004

• Multicenter retrospective cohort study
• EC pts with first line platinum-based therapy (excluding chemo/RT) who received second-line platinum therapy at time of recurrence
  – 262 patients, 30 centers
  – FIGO stage I (29) II (23) III (122) IV (88)
  – Endometrioid (153) serous (34) clear cell (17) carcinosarcoma (36) other (22)

Nagao et al Gynecol Oncol 131:567, 2013
RR(%) to Second-line Platinum Therapy by Platinum-Free Interval

Nagao et al. Gynecol Oncol 131:567, 2013
Fig. 1. Estimates of (A) progression-free survival and (B) overall survival after second-line platinum-based chemotherapy for patients classified on the basis of platinum-free interval (all participants). PFI, platinum-free interval; PFS,


Applicability of the concept of “platinum sensitivity” to recurrent endometrial cancer: The SGSG-012/GOTIC-004/Intergroup study


http://dx.doi.org/10.1016/j.ygyno.2013.09.021
Case Study #1

• 65 y/o Filipino woman
  – 6/2013 TAH/BSO for grade 3 deeply invasive (2/9/3.0 cm) endometrioid adenocarcinoma +LVSI
    • Treated with carbo/paclitaxel x 6
  – 10/2013 vaginal nodule noted on pelvic exam
    • EBRT/VBT
  – 10/2015 pelvic pain, 5 cm rectovaginal mass, hyperintense on PET scan, tumor fixed to left pelvic sidewall on exam
Case Study #1

- Tumor genomic profiling showed MSI-hi
- ER/PR weak/variable
- Three separate surgical opinions suggested borderline resectability
  - Immunotherapy?
  - Surgery? (after chemotherapy?)
  - Chemotherapy? Endocrine therapy?
    - Taxane/platinum?
    - Doxorubicin?
    - Bevacizumab?
Case Study #1

- Pt desired immunotherapy, but not eligible for available clinical trials
- Pt refused bevacizumab for fear of toxicity
- Refused surgery as did not wish colostomy
- Received six cycles of carboplatin/paclitaxel with CR on imaging and exam, remains in CR @18 mos
Endometrial cancer TCGA, 2013

Histologic breakdown:
- Type I (hyperE2, metabolic synd)
- Type 2 (p53mut, serous)

Molecular breakdown
- POLE ultramutated
- MSI hi hypermutated
- CNV low (endometrioid)
- CNV hi (serous-like)
Responses in Mismatch Repair Deficient Cancers (ASCO 2015)

- MMR-proficient CRC
- MMR-deficient CRC
- MMR-deficient non-CRC

Days
%Change from Baseline SLD

MMR-proficient CRC
MMR-deficient CRC
MMR-deficient non-CRC
Durability of Disease Control

Graph showing the percentage change from baseline SLD over time for different types of diseases:
- Endometrial
- Ampullary/biliary
- Pancreatic
- Small bowel
- Gastric
- Prostate
- Sarcoma

Graph axes:
- X-axis: Days
- Y-axis: % Change from Baseline SLD
On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This is the FDA’s first tissue/site-agnostic approval.
Hormonal Therapy for Advanced/Recurrent Endometrial Cancer

• Progestin-based therapy in the front-line setting yields response rates of 15-25% with median survivals of 12-14 mos

• Tumors that are low grade and ER/PR positive have higher response rates

• Primary endocrine-based therapy remains appropriate for suitable patients!
  – Effort should be expended to determine who will respond
  – Addition of mTOR inhibitors and CDK 4,6 inhibitors (viz breast cancer) promising
A Randomized Phase II Trial of Everolimus and Letrozole or Hormonal Therapy (Tamoxifen/Medroxyprogesterone Acetate) in Women with Advanced, Persistent, or Recurrent Endometrial Carcinoma

GOG 3007

Arm 1
Everolimus
10 mg daily
Letrozole
2.5 mg PO daily
One cycle = 28 days

Arm 2
Tamoxifen
20 mg PO bid days 1-28
Medroxyprogesterone Acetate
200mg PO (days 8-14 and 22-28)
One cycle = 28 days

Until progression of disease or adverse effects prohibit further therapy.

Advanced (stage III or IV) persistent or recurrent measurable endometrial carcinoma which is not likely to be curable by surgery or radiotherapy.

Opened 2/19/2015
Case Study #2

• 70 y/o woman with 2009 TAH/BSO/LND for carcinosarcoma +LVSI, nodes negative treated with RT + taxol/ifos x 4

• 2015 recurred with SBO, 9 cm suprarenal mass, multiple 2-3 cm lung metastases
  – SBO resolved with conservative measures
  – BX poorly differentiated adenocarcinoma
  – U of C reread of original gr3 adenocarcinoma
Case Study #2

- Pt refused chemotherapy
- Tumor ER/PR strongly and diffusely positive
- Treated with provera/tamoxifen for 2 years, had PR, just progressed.
  - Genomic profiling pending
First line treatment for Recurrent/Metastatic Endometrial Cancer

• Endocrine therapy should be used first in appropriate patients
  – ER/PR status via IHC should be used (opinion)
• Chemotherapy remains best option for almost everyone else
• Immunotherapy, alone or with chemotherapy is likely to be first-line soon for MSI hi tumors
  – Mismatch repair IHC should be universal (opinion)
• At this time genomic profiling has nothing superior to offer the vast majority of women (and it adds to cost)