Ovarian Cancer

Stuart M. Lichtman, MD
Attending Physician
65+ Clinical Geriatric Program/Gynecologic Oncology DMT
GOG Elderly Patient Taskforce
Memorial Sloan-Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College

Clinical Trials

• Median age at diagnosis 64 years
• There have been no prospective randomized trials of older women in any gynecologic cancer
• Need to extrapolate from trials in which older patients make up small percentage of patients
  – Usually shows feasibility
• Few small (<50 pts) phase II in older patients

Treatment Outline

• Primary surgical debulking
  – Optimal (no residual; <1 cm) vs. suboptimal
• Chemotherapy
  – IV
  – IP only for optimal patients

Advanced Ovarian Cancer over 65 Years

• Older women have poorer survival
  – Possible causes:
    • Delay in diagnosis
    • Poor surgery
    • Undertreatment: more often chemotherapy delay; less chemotherapy
    • Biology
  – Platinum based therapy effective

MSKCC: Advanced Ovarian Cancer by Age (Retrospective)

• No difference:
  – PFS
  – OS
  – Chemotherapy regimens
  – Chemotherapy dose administered
  – Chemotherapy toxicity


Primary Therapy: 2012
Ovarian Cancer Landmarks in Therapy
1. Young, et al, showed combinations superior to single agent, 1978
2. Cisplatin effective in refractory disease
3. Carboplatin equivalent to cisplatin with less toxicity (Calvert formula)
4. Paclitaxel effective in platinum refractory patients
5. GOG 111: paclitaxel-cisplatin superior to cyclophosphamide-cisplatin
6. GOG 158: Paclitaxel-Carboplatin superior to paclitaxel-cisplatin; second look surgery not beneficial
7. GOG 182: 3 drugs vs. paclitaxel/carboplatin

GOG182: Ovarian Cancer (Stage III-IV)

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>CP</th>
<th>CFG</th>
<th>OPD</th>
<th>CT+CP</th>
<th>CG+CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 604)</td>
<td>n = 594</td>
<td>(n = 602)</td>
<td>(n = 601)</td>
<td>(n = 601)</td>
<td></td>
</tr>
<tr>
<td><strong>Patient Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Age (yr)</td>
<td>57.7</td>
<td>59.1</td>
<td>59.5</td>
<td>59.5</td>
<td>59.3</td>
</tr>
<tr>
<td>PGO Stage 3 (%)</td>
<td>83.6</td>
<td>88.7</td>
<td>86.2</td>
<td>86.4</td>
<td>83.7</td>
</tr>
<tr>
<td>PGO 4 (%)</td>
<td>16.2</td>
<td>13.3</td>
<td>13.8</td>
<td>13.7</td>
<td>16.3</td>
</tr>
</tbody>
</table>

Conclusions:
- Median Age = 59
- No survival improvement with a third agent.
- Carboplatin + Paclitaxel (CP) remains standard first-line treatment.

Issues in Primary Therapy
- Primary surgery vs. neoadjuvant therapy
- Role of intraperitoneal therapy; are there alternatives?
  - New drugs
  - Drug scheduling
- Role of bevacizumab

JGOG: Phase III IV paclitaxel and carboplatin vs. dose dense (TC-T-T)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Median PFS</th>
<th>P-value HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>259</td>
<td>17.2 mos</td>
<td>0.012</td>
<td>0.81-1.26</td>
</tr>
<tr>
<td>TC-T-T</td>
<td>259</td>
<td>21.6 mos</td>
<td>0.01</td>
<td>0.81-1.26</td>
</tr>
</tbody>
</table>


GOG 172: Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer
- Intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel improves survival in patients with optimally debulked stage III ovarian cancer:
  - Progression-free survival 18.3 vs. 23.8 months
  - Overall survival 49.7 vs. 65.6 months
- QOL decreased in IP arm, but equivalent at 12 months
- Markedly increased treatment related toxicity; patient selection important
- Work intensive; need experience

Armstrong, et al, 2006
Primary Therapy
Weekly Therapy

• Eligibility
  – Patients aged ≥70 years
  – Stage IC-IV ovarian cancer,
  – Performance status ≤2

• Treatment
  – Carboplatin (AUC 2) + paclitaxel (60 mg/m²) on days 1, 8, 15
  every 4 weeks, up to six cycles

• Results
  – PFS 13.6 months
  – Acceptable toxicity

Pignata, et al 2008

New Drug

• IP Carboplatin

• Should IP carboplatin be substituted for IP cisplatin due to issues of toxicity?

New Drug:
Bevacizumab (Avastin)

Not FDA approved for any gynecologic malignancy

Bevacizumab: Randomized Trials

• Primary Therapy
  – paclitaxel/Carboplatin +/- bevacizumab
    • GOG 218
    • ICON 7

Phase III GOG 218/ICON 7: Many Questions

• Will there be an overall survival benefit?
• Could it be given with same benefit later in disease course?
• How long should it be administered? Until PD? For life?
• What will the phenotype of relapsed disease look like? Is there rebound?
• What is the required dose? Is less equally effective?
GOG 0252 (optimal)

Stage II or III
(>1cm residual), Ovarian, primary peritoneal, or fallopian tube cancer

**Randomize**

- Paclitaxel 80 mg/m²/1h IV, Days 1, 8, 15, Cycles 1-6
  - Carboplatin AUC 6 IV, Day 1, Cycles 1-6
  - Bevacizumab 15 mg/kg IV, Cycles 2-22

- Paclitaxel 80 mg/m²/1h IV, Days 1, 8, 15, Cycles 1-6
  - Carboplatin AUC 6 IP, Day 1, Cycles 1-6
  - Bevacizumab 15 mg/kg IV, Cycles 2-22

- Paclitaxel 135 mg/m²/3h IV, Day 1, Cycles 1-6
  - Cisplatin 75 mg/m² IP, Day 2, Cycles 1-6
  - Paclitaxel 60 mg/m² IP, Day 8, Cycles 1-6
  - Bevacizumab 15 mg/kg IV, Cycles 2-22

Ovarian Cancer 2012

- Carboplatin and paclitaxel (or docetaxel) remain a standard of care (GOG 182)
- 3 randomized trials have shown a superiority for survival using IP therapy in optimal patients.
- IP regimen requires modification for toxicity.
- IV Bevacizumab prolongs PFS in first line therapy.
- JGOG suggests impact of paclitaxel schedule
  - Weekly therapy for older patients or limited to those who are vulnerable
- GOG 252 will answer some of these questions

Considerations in Older Patients

- Neoadjuvant chemotherapy vs. primary surgery
  - Can we identify the patient appropriate for neoadjuvant chemotherapy?
    - Over 80 years of age
    - Multiple comorbidities
    - Poor PS
    - Tumor bulk
    - Prospective study of geriatric assessment

McLean KA, et al. Gynecol Oncol, 2010

Chemotherapy
Treatment Outcomes for Older Women with Advanced Ovarian Cancer: Phase III Clinical Trial (GOG182)

William Tew, Jim Java, Dennis Chi, Andrew Menzin, John Lovecchio, Michael Bookman, and Stuart Lichtman
Memorial Sloan-Kettering Cancer Ctr, NY, NY; Gynecologic Oncology Group, Buffalo, NY; Memorial Sloan-Kettering Cancer Ctr, NY, NY; North Shore Univ Hosp, Manhasset, NY; Arizona Cancer Center, Tucson, AZ; Memorial Sloan-Kettering Cancer Ctr, NY, NY

GOG 182
• Patients ≥ 70yo = 620 (17%)
• Overall survival differences (older vs. younger):
  • 37.2 vs. 45 months (p<0.001)
• PFS: 16 vs. 15 months; ?treatment at relapse
• Non-cancer death rate:
  • 13% vs. 7% (p<0.001)
• Relative risk of cancer-specific death:
  • RR = 1.14 (95% CI, 1.01-1.27, p =0.028)
• Survival differences observed in first 12-months

Women with ovarian cancer ≥ 70yo:
• Poorer performance status
• Less likely to complete 8 cycles of chemo
• More toxicity (neuropathy, cytopenia)
  • Similar to paclitaxel in breast cancer*
  • Similar optimal debulking rates, but longer post-operative recovery
• Do we need elderly specific trials?


Intraperitoneal Regimen: Should Older Patients Receive IP Therapy?

IP Therapy by Age: MSKCC

Survival

Toxicity


Ovarian Cancer: Alternatives
• Frail
• Multiple comorbidities
• Poor performance status
  • These represent different patient populations
• Weekly paclitaxel/carboplatin (not consecutive)
• Single agent, i.e. carboplatin or paclitaxel
• Liposomal doxorubicin/carboplatin (as per CALYPSO)

Pignata, et al. 2008
The next step...

GOG 273: Ovarian Cancer in the Older Patients

- Liberal eligibility criteria
- Patient and physician therapy choices—not randomized
- Prospective geriatric assessment
- Allows neoadjuvant

Conclusion

- Older patients with adequate performance status and functional status should receive current standard of care
- Encourage participation in clinical trials
- Off study
  - Consider intraperitoneal regimen
  - Standard IV paclitaxel/carboplatin
- Neoadjuvant chemotherapy may provide time to optimize patients for surgical resection

Thank you