Do All Patients with Recurrent Ovarian Cancer Need Systemic Therapy?

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Outline of presentation

• Guiding Principles for systemic treatment in ROC
• *Chemotherapy in the last weeks of life*
• Focus on 3 clinical scenarios
  “Platinum resistant” ovarian cancer
  ➢ Problem basing decisions on a loose “definition”
  ➢ Factors to take into consideration
  ➢ Identifying patients with a very short survival- prognostic tools

Special Subtypes- Mucinous/Clear Cell/ Low Grade Serous

Asymptomatic patients with CA125 progression after 1\textsuperscript{st} line
Guiding Principles
Treating patients with Recurrent Ovarian Cancer

• Don’t treat patients in last weeks of life

• Don’t offer systemic therapy to patients who are unlikely to benefit

• Cease treatment if no clinical benefit

• Avoid/ cease systemic therapy where risk of toxicity >> any benefit

• Treat patients with recurrent ovarian cancer who are likely to benefit
Reasons for offering systemic therapy

➢ Clinical - based on patient/tumor related factors
  • Consider that patient likely to benefit- qualitative /quantitative

➢ Patient -desire for more treatment ?
  – Doing something is better than nothing
  – Some patients will accept treatment even if the benefit is very low
  – Treatment = hope

Underpinned by clear communication re likely prognosis and chance of benefit
Clinicians expectations of treatment in the Symptom Benefit Study

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>MEDIAN</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated likelihood of response</td>
<td>30%</td>
<td>0-100%</td>
</tr>
<tr>
<td>Estimated likelihood of symptom benefit</td>
<td>40%</td>
<td>0-100%</td>
</tr>
<tr>
<td>Estimated survival (months)</td>
<td>12</td>
<td>3-70</td>
</tr>
<tr>
<td>Estimated number of cycles to be administered</td>
<td>6</td>
<td>2-52</td>
</tr>
<tr>
<td>PRR – number of cycles received</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>PPS&gt;3 – number of cycles received</td>
<td>3.8</td>
<td></td>
</tr>
</tbody>
</table>

• 89% of patients were “ECOG 0-1”.
• 26% of patients with PR-ROC had < 8 weeks of chemotherapy
• Rapid progression/death- main reason for < 8 weeks treatment

> 70 % of patients expected a significant reduction in symptoms with chemotherapy

Systemic therapy

Questionable benefit if:

- Progression on > 3 lines of treatment?
- Significant Functional and Physical impairment - QLQC30
- Significant abdominal /gastrointestinal symptoms - cramping/intermittent bowel obstruction
- Low serum albumen and high inflammatory markers
- Large volume disease
- Multiple metastatic sites

Commonly many of these are present simultaneously
Chemotherapy in last weeks of life

• ASCO identified stopping end of life chemotherapy as one of the “top five” practices that could improve patients’ care and reduce costs
• 20-50% of patients with advanced cancers receive chemotherapy within 30 days of death
• Deciding when to discontinue chemotherapy is often challenging for clinicians and patients
• Patients who received concurrent palliative treatment stopped chemotherapy ~ 2 months earlier than those in the standard oncology group- but had a longer median overall survival.
• Discussion about their preferences for end of life care associated with less aggressive care including chemotherapy near death

Figure 2 Change in the use of chemotherapy over the course of the last 3 months before death, by age at time of death and number of Charlson comorbidities. Crude (unadjusted) proportions.

Age dependent proportions.
Do All Patients with Recurrent Ovarian Cancer Need (Benefit from) Systemic Therapy?

3 Clinical Scenarios

“Platinum Resistant” Ovarian Cancer

Special Types
- Clear Cell
- Mucinous
- Low Grade Serous

Asymptomatic CA125 progression after 1st line Rx

Excluding the frail elderly / patients with multiple medical comorbidities/poor performance status
Identifying frail elderly and patients with significant co-morbidities

Treating the elderly - Geriatric Assessment and Frailty scores

Patients with comorbidities - Charlson Comorbidity Index

Charlson Comorbidity Index (CCI) – MDCal. https://www.mdcalc.com/charlson-comorbidity-index-cci

Cancer 2012 Jul 1;118(13):3377-86


Selecting patients with recurrent ovarian cancer for systemic treatment

Identifying patients who are most likely to gain benefit
The impact of second to sixth line therapy on time to treatment failure and survival of relapsed ovarian cancer - LINES OF TREATMENT

TCGA data

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Median TT (months)</th>
<th>P*</th>
</tr>
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<tbody>
<tr>
<td>First line</td>
<td>402</td>
<td>14.8</td>
</tr>
<tr>
<td>Second line</td>
<td>181</td>
<td>10.2</td>
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<tr>
<td>Third line</td>
<td>108</td>
<td>5.7</td>
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<tr>
<td>Fourth line</td>
<td>76</td>
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<td>Fifth line</td>
<td>58</td>
<td>5.1</td>
</tr>
<tr>
<td>Sixth line</td>
<td>36</td>
<td>3.7</td>
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</table>

HGSC

The Law of Diminishing Returns

Villalobos VM JCO Clinical Cancer Informatics 2018 :2, 1-16

Platinum Resistant Ovarian Cancer

**ORR 10%; Median PFS 3 months; Median OS 10-12 months**

- Definition mired with problems
- GOG in the 1980's defined platinum resistant as "patients who progressed while receiving platinum based chemotherapy or whose best response to platinum was SD and who progressed within 6 months of platinum based chemotherapy" - selection criteria for Phase 2 trials
- Gradually “morphed” into what is used today - which is quite different and simply defines PROC as progression within 1-6 months of 1st line (or any line...).
Problems with a time dependent label

Recurrence at 4 months post 1st line- All could be classified as PROC

CA125 progression alone

PET scan only

All PRROC
But
Very different

Symptomatic ascites

Bowel Obstruction
PFS6/ ORR in patients classified as **Platinum Resistant** enrolled in Phase 2 trials

- 74 Trials with 3270 patients included
- PFS ranged from 1 month to 10 months
- PFS6 4-74%
- ORR ranged from 0-64%
- Median Survival ranged 10 – 15 months (range 2 -36 months)

Underscores the patient heterogeneity and problems with the definition of “platinum resistance” to predict outcomes

Platinum Resistant Ovarian Cancer
Factors to Consider in individual Patient

- Rate of Progression
- Symptomatic vs. Asymptomatic
- Physical Functioning
- Bowel Obstruction
- Intermittent cramping abdominal pain
- Volume and Sites of Recurrence

Histological Subtype
- BRCA mutation

How Recurrence Detected
- Number of Lines of Prior treatment

Prognostic Factors-
- Inflammatory Markers
- Haemoglobin
- Thrombocytosis
- Physical Functioning
- Bowel Obstruction
- Intermittent cramping abdominal pain
- Volume and Sites of Recurrence
PFS and OS in the GCIG Symptom Benefit Study

Resistant/Refractory (N= 570)

Progression Free Survival (%)

Time (months) since registration

Number at Risk: 570 408 249 162 96 61 41 32 21 13 10 6 2

Overall Survival (%)

Time (months) since registration

Number at Risk: 570 479 379 289 222 168 130 100 63 43 31 19 10
Platinum Resistant Ovarian Cancer
Heterogeneous Group of Patients

Hypothetical Risk Categorisation
GLASGOW PROGNOSTIC SCORE TO PREDICT OS IN PROC

mGPS is based on **serum C reactive protein** and **albumin**, with scores ranging from 0 (least) to 2 (most)

Roncalato et al Gynecol Oncol. 2018 Jan;148(1):36-41
Predictors Survival in Platinum Resistant/Refractory Ovarian Cancer - The GCIG Symptom Benefit Study

HRQOL

QLQC30

Figure 1. Kaplan-Meier curves for overall survival by quality of life domain.
Platinum resistant recurrent ovarian cancer

Overall Survival

A tool for researcher and health care professionals to prognosticate overall survival outcomes in patients with platinum resistant recurrent ovarian cancer treated with chemotherapy.

Your Patient Characteristics at Disease Relapse

- Performance status
- Ascites
- CA125
- Largest tumor size
- Platinum resistance
- Platinum-free interval

Submit

Result

Patient risk: High risk

Predicted Probability of Overall Survival at 12 months: 26.19%

Predicted median Overall Survival: 6 Months

Best case scenario: Best 10 out of 100 similar women would live for 19 Months

Worst case scenario: Worst 10 out of 100 similar women would live for less than 3 Months

Typical range: middle 50 of 100 similar women would live for somewhere between 12 Months and 3 Months

proconline.ctc.usyd.edu.au

Lee et al
Journal of Clinical Oncology 2015 33: 15: 5547-5547
Consideration of Histotype and Outcomes

• Mucinous Ovarian Cancer
  Rare – 4%

• Clear Cell Ovarian Cancer
  Rare – 15%

Recurrent/Metastatic disease
  – low response rates
  – short duration of benefit
  – frequently refractory to first line therapy
  – Platinum based therapies limited benefit
  – Definitions of platinum sensitivity/ resistance not be relevant

➢ Low Grade Serous Cancers
  6–10% of serous ovarian cancer- younger patients- low response rates
Mucinous Cancers

• Very limited data on response to treatment of recurrent mucinous ovarian cancers - (rare 44/4000 in GOG182)
• “Most” data is for 1st line therapy – advanced stage
• Hess et al 26% RR in 1st line 27 cases
• BCCA - N=53, Stage IIIA-IV and/or recurrent
  44 cases evaluable for response “any” degree of benefit (lack of progression) = 8/44 = 18%
• Socrates trial- 20 patients – retrospective survey 36% RR

Chemotherapy for recurrent clear cell ovarian cancer

<table>
<thead>
<tr>
<th>Rx</th>
<th>N</th>
<th>Plt Sensitive</th>
<th>No. evaluable</th>
<th>CR/PR%</th>
<th>CBR%</th>
<th>Median PFS wks</th>
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<tbody>
<tr>
<td>Plt-based</td>
<td>63</td>
<td>Yes (46)</td>
<td>38</td>
<td>18</td>
<td>39</td>
<td>17</td>
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<td></td>
<td></td>
<td>No (17)</td>
<td>14</td>
<td>14</td>
<td>36</td>
<td>11</td>
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<tr>
<td>Paclitaxel</td>
<td>8</td>
<td>7</td>
<td>0</td>
<td></td>
<td>14</td>
<td>8</td>
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<tr>
<td>Gemcitabine</td>
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<td>7</td>
<td>14</td>
<td></td>
<td>14</td>
<td>4</td>
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<tr>
<td>Doxorubicin</td>
<td>29</td>
<td>25</td>
<td>4</td>
<td></td>
<td>16</td>
<td>10</td>
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<tr>
<td>Topoisomerase inhibitors</td>
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<td>27</td>
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<td>19</td>
<td>8</td>
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<td>Hormonal therapy</td>
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<td>6</td>
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<td>17</td>
<td>12</td>
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<tr>
<td>Others</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td></td>
<td>0</td>
<td>11</td>
</tr>
</tbody>
</table>

At 1st relapse - \( \text{RR}=14\% (10/72) \) and median PFS=12wks
At 2nd relapse- \( \text{RR}=8\% (3/36) \)and median PFS=14wks

Tan D et al Journal of Clinical Oncology 32, no. 15_suppl (May 2014) 5548-5548
In a report of 58 women who received 108 separate chemotherapy regimens for recurrent LGSC, the response rate was 3.7% (4.9% in patients with platinum-sensitive disease and 2.1% in those with platinum-resistant disease)

The benefit of systemic therapy is limited and questionable for most patients.

Options - Clinical trials / hormonal therapies

Discussing prognosis

• Helps patients and their families make decisions
• Reduces the number of patients who opt for more systemic therapy
• Facilitates advanced care directives- less invasive procedures at end of life
• Earlier initiation of palliative care- improves symptom control and possibly survival
• Better quality of life in final months of life
• More likely to die at home rather than in hospital
• Reduces burden on carers
Expected and Perceived Benefit

How much do you expect your symptoms to improve with chemotherapy? (Baseline)

How much have your symptoms improved with chemotherapy? (Prior to Cycle 3)

And now- Something completely different!
Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial

Lancet 2010; 376: 1155-1163

Gordon J S Rustin, Maria E L van der Burg, Clare L Griffin, David Guthrie, Alan Lamont, Gordon C Jayson, Gunnar Kristensen, César Mediola, Corneel Coens, Wendi Qian, Mahesh K B Parmar, Ann Marie Swart, for the MRC OV05 and EORTC 55955 investigators*

No survival advantage with early chemotherapy in patients with CA125 progression following complete radiological and biochemical remission after 1st line treatment

Median survival ~ 2 years

Opened for recruitment in 1997 - closed March 2008 1442 registered 529 randomised
CA 125 surveillance of uncertain value- *don’t treat asymptomatic patients with CA125 progression alone*

Follow-up of patients who are clinically disease-free after primary treatment for fallopian tube, primary peritoneal, or epithelial ovarian cancer: a Program in Evidence-Based Care guideline adaptation

We recommend that survivors be made aware of the potential harms and benefits of surveillance, including a discussion of the limitations of CA125 testing. Women could be offered the option of no formal follow-up or a follow-up schedule that is agreed upon by the woman and her health care provider.

Current Oncology 2016 : 23 ; 5 ; 343-350

**Society Position Statements/White Papers**

An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations

2017 Gynecol Oncol

Ritu Salani a,*, Namita Khanna b, Marina Frimer c, Robert E. Bristow d, Lee-may Chen e

**CA 125 surveillance of uncertain value- optional**
MRC OV05/EORTC 55955 trial of early vs delayed chemotherapy

- Patients randomized to early treatment started chemotherapy 4.8 months (95% CI 3.6-5.3) earlier than those allocated to delayed treatment
- Two thirds of patients received monotherapy at recurrence
- Secondary cytoreduction was performed rarely
- Following second line treatment- 67% of patients assigned to early and 54% assigned to delayed treatment received 3rd line chemotherapy

- 65% of patients had HGSC No BRCA testing
Factors to consider

- Median time between CA125 progression and symptoms is 3-4 months
- Progression can be rapid
- Patients with smaller volume disease have a higher likelihood of response and longer PFS and OS with second line treatments
- Better tolerance of treatment in patients without functional/physical impairment
- New era of maintenance therapy with PARP inhibitors in HGSC
- Patients who have a CR to 2ND line platinum based chemotherapy have a significantly longer PFS with maintenance PARP inhibitors
- Time to reconsider timing of treatment?
Nomogram to predict PFS in patients with “platinum sensitive” recurrent ovarian cancer

Points

Largest tumour size
- Non-measurable
- <5 cm
- >5 cm

Last platinum chemotherapy (months)
- >12
- 6–12
- <6

CA-125 (IU ml\(^{-1}\))
- >100
- ≤100

Number of organ sites of metastases
- >1
- ≤1

White blood cell (×10\(^9\) per l)
- >6
- ≤6

Total points

Median PFS (months)

Probability of 12-month PFS
Do All Patients with Recurrent Ovarian Cancer Need Systemic Therapy?

• **NO!**

• After taking age/frailty and co-morbidities into consideration - there are a subset of patients with ROC who will not benefit from systemic therapy.

• Treating patients in last weeks of life should be avoided.

• The challenge is how to identify poor risk patients - number of factors that need to be considered beyond a simple definition of platinum resistance - tools are available to help.

• Specific subtypes HGSC vs other histotypes - impacts on response.

• Reconsider timing of treatment in asymptomatic patients with HGSC with CA125 progression alone - case for earlier treatment rather than wait for symptoms.