ESMO-ESO COURSE FOR MEDICAL STUDENTS

18-23 JULY 2019, VALENCIA

OVARIAN CANCER- DIAGNOSIS, STAGING AND THERAPY

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ESMO Council Member
- Personal financial interests:
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- Institutional financial interest (clinical trials/contracted research): Amgen, Astex, Astrazeneca, Aprea, Array, Astellas, Bristol Myer Squibb, Clovis, Endocyte, Enita, Glycotope, Roche, Genentech, GlaxoSmithLine, Immunogen, Lilly, Medimmune, Merck, Merck Sharpe Dhome, Millenium, Nucana, Pfizer, Pharmamar, Takeda, Tesaro
OVERVIEW

Ovarian Cancer Diagnosis
Ovarian Cancer Management
  ● Investigations
  ● Staging
  ● First Line Treatment- Surgery, Chemotherapy
  ● Treatment for Recurrence
  ● Novel Drugs for Ovarian Cancer
OVARIAN CANCER- BACKGROUND

- 250 000 diagnosed each year globally; 140 000 deaths
- 7th most common cancer in women; 6th most common cause of death globally
- Almost 43 000 deaths/year in Europe
- Europe has the highest rates of ovarian cancer in the world
- Ovarian cancer is a challenge to diagnose because of the non-specific nature of symptoms and signs
- Most women are diagnosed with advanced disease (stages II–IV)

http://worldovariancancercoalition.org/#cancer
## Gynaecological Cancers

### Incidence and deaths in UK

<table>
<thead>
<tr>
<th></th>
<th>Incidence 2015</th>
<th>Deaths 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>55,112</td>
<td>11,563</td>
</tr>
<tr>
<td>Ovary</td>
<td>7,270</td>
<td>4,227</td>
</tr>
<tr>
<td>Uterus</td>
<td>8,984</td>
<td>2,360</td>
</tr>
<tr>
<td>Cervix</td>
<td>3,126</td>
<td>854</td>
</tr>
</tbody>
</table>

CRUK statistics
## Ovarian Cancer - Survival Rates

<table>
<thead>
<tr>
<th>Stage at diagnosis</th>
<th>% of all cases</th>
<th>5-year relative survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>29</td>
<td>92.0</td>
</tr>
<tr>
<td>Stage II</td>
<td>4</td>
<td>55.1</td>
</tr>
<tr>
<td>Stage III</td>
<td>45</td>
<td>21.9</td>
</tr>
<tr>
<td>Stage IV</td>
<td>15</td>
<td>5.6</td>
</tr>
<tr>
<td>Unstaged</td>
<td>6</td>
<td>27.6</td>
</tr>
<tr>
<td>All stages</td>
<td>100</td>
<td>43.5</td>
</tr>
</tbody>
</table>
### Ovarian Cancer-Risk Factors

The majority of women have no known risk factors. Most significant risk factor is genetic predisposition.

#### Risks
- Age
- BRCA mutations
  - BRCA 1 60%, BRCA 2 27% lifetime risk of ovarian cancer compared to <4%
- Family history breast/ovary
- HRT >5yrs
- Fertility treatment
- Endometriosis

#### Protective factors
- OCP
- Parity
- Breast feeding
- Tubal surgery

#### Relative Risk for Ovarian Cancer by Parity

<table>
<thead>
<tr>
<th>Number of children</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1.21 (1.10-1.32)</td>
</tr>
<tr>
<td>1</td>
<td>1.60 (1.43-1.79)</td>
</tr>
<tr>
<td>0</td>
<td>2.12 (1.81-2.48)</td>
</tr>
</tbody>
</table>

#### Relative Risk for Ovarian Cancer by Duration of Oral Contraceptive (OC) Use (mean)

<table>
<thead>
<tr>
<th>OC use</th>
<th>Relative risk (99% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1.0 (0.96-1.04)</td>
</tr>
<tr>
<td>Less than 1 year (0.4 years)</td>
<td>1.0 (0.91-1.10)</td>
</tr>
<tr>
<td>1)4 years (2.4 years)</td>
<td>0.78 (0.73-0.83)</td>
</tr>
<tr>
<td>5)9 years (6.8 years)</td>
<td>0.64 (0.59-0.69)</td>
</tr>
<tr>
<td>10)14 years (11.16 years)</td>
<td>0.56 (0.50-0.62)</td>
</tr>
<tr>
<td>15 years or more (18.3 years)</td>
<td>0.42 (0.35-0.49)</td>
</tr>
</tbody>
</table>

#### Risk Reduction per 5 years of OC Use

<table>
<thead>
<tr>
<th>Time elapsed since cease</th>
<th>Proportional risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 10 years</td>
<td>29%</td>
</tr>
<tr>
<td>10)19 years</td>
<td>19%</td>
</tr>
<tr>
<td>20)29 years</td>
<td>15%</td>
</tr>
</tbody>
</table>

* Relative risk stratified by study, age, parity, and hysterectomy.

OVARIAN CANCER- DISEASE OF MANY SUBTYPES

- **Epithelial**
  - High-grade serous
    - TP53, BRCA1 and 2, NF1, RB1, CDK12
    - Homologous recombination repair genes*
  - Low-grade serous
  - Mucinous
    - KRAS, HER2 amplification
  - Clear cell
    - ARID1A, PIK3CA, PTEN, CTNNB1, PPP2R1α
  - Endometrioid
    - ARID1A, PIK3CA, PTEN, PPP2R1α
    - MMR deficiency

- **Nonepithelial**
  - Sex cord-stromal
    - Granulosa cell, FOXL2
  - Others, including germ cell
    - Sertoli-Leydig cell, DICER1

*Pathway alterations: PI3K/RAS/NOTCH/FOXM1

© 2013 American Association for Cancer Research

**CCR New Strategies**

Banerjee and Kaye Clin Can Res 2013
OVARIAN CANCER-DIAGNOSIS

WHY MISSED OR DELAYED?

– Lack of severity and specificity of early symptoms
  signs/symptoms include
  – bloating
  – abdominal fullness/discomfort
  – urinary frequency/pelvic pressure
  – fatigue
  – vomiting

  -indigestion
  -constipation
  -abnormal vaginal bleeding
  -back pain
  -short of breath

◆ Misdiagnosed Irritable Bowel Syndrome or gastritis
◆ If cancer considered often referral wrong investigative pathway and delay treatment

LACK OF AWARENESS
WHY DOES IT MATTER?

- Most women present at advanced stage with overall 5 yr survival 20% or less
- In early stage 5 yr survival 80-90%

- Median time to diagnosis:
  - < 3 mnths 55%
  - > 6 mnths 26%
  - > 12 mnths 11%

- GP with average practice will see 1 ovarian cancer case every 5 years
- Early diagnosis difficult
- No relationship between duration symptoms and survival
- Women presenting with advanced ovarian cancer experience same duration of symptoms to those presenting with early stage ovarian cancer
History (age, menopausal status, symptoms, family history)
Pelvic Exam (including rectal)
Transvaginal Ultrasound
Blood Test: tumour markers, CA-125
CONDITIONS ASSOCIATED WITH RAISED CA-125

Malignant conditions
- Cervical
- Fallopian tube
- Endometrial
- Pancreatic
- Colon
- Breast
- Lung

Benign conditions
- Endometriosis/Menses
- Uterine fibroids
- PID
- Pregnancy
- Diverticulitis
- Pancreatitis
- Liver disease
- Renal failure
- Appendicitis
- IBD
Overview of ovarian cancer pathway

Women presents to GP

GP assesses symptoms

Tests in primary care

Urgent referral: assessment in secondary care

Review by specialist multidisciplinary team (MDT)

Confirmation of diagnosis:
- surgical staging or
- tissue diagnosis by histology (preferably) or cytology if considering chemotherapy before or instead of surgery for advanced ovarian cancer

Management of suspected early ovarian cancer

Management of advanced ovarian cancer

Support and information

Ascites and/or pelvic or abdominal mass
Awareness of symptoms and signs

Carry out tests in primary care if a woman (especially if 50 or over) reports having any of the following symptoms on a persistent or frequent basis – particularly more than 12 times per month:

– persistent abdominal distension (women often refer to this as ‘bloating’)
– feeling full and/or loss of appetite
– pelvic or abdominal pain
– increased urinary urgency and/or frequency

NICE Guidelines 2011
Awareness of symptoms and signs

Carry out tests in primary care if a woman (especially if 50 or over) reports having any of the following symptoms on a persistent or frequent basis – particularly more than 12 times per month:

– persistent abdominal distension (women often refer to this as ‘bloating’)
– feeling full and/or loss of appetite
– pelvic or abdominal pain
– increased urinary urgency and/or frequency

• Consider carrying out tests in primary care if a woman reports unexplained weight loss, fatigue or changes in bowel habit

• Carry out appropriate tests for ovarian cancer in any woman of 50 or over who has experienced symptoms within the last 12 months that suggest irritable bowel syndrome (IBS)

• Advise any woman who is not suspected of having ovarian cancer to return to her GP if her symptoms become more frequent and/or persistent

NICE Guidelines 2011
First tests in primary care

Measure serum CA125

- 35 IU/ml or greater
  - Ultrasound of abdomen and pelvis
    - Suggestive of ovarian cancer
      - Refer urgently
    - Normal
      - Advise to return to GP if symptoms become more frequent and/or persistent

- Less than 35 IU/ml
  - Assess carefully: are other clinical causes of symptoms apparent?
    - Yes
      - Investigate
    - No
      - Advise to return to GP if symptoms become more frequent and/or persistent

Normal
Malignancy indices

• Perform ultrasound

• Calculate a risk of malignancy index I (RMI I) score

• Refer all women with an RMI I score of 250 to specialist team

• Refer urgently if ascites and/or pelvic or abdominal mass (no obvious fibroids)

Risk of Malignancy Index

= U x M x CA125

- U=0; U=1 (score 1); U=2 (score of 2-5)
  1 point for: multilocular cyst; solid areas; evidence of mets; ascites; bilateral lesions
- M=3 for all postmenopausal women
- Ca-125 serum measurement
OVARIAN CANCER - SCREENING

So far CA-125 and Pelvic Ultrasound are not routine screening tests
Large study recently reported in Lancet Dec 2015- UKCTOCS
Multimodal- CA125 yearly and US or US only
More early stage cancers detected with multimodal approach

For every woman found to have ovarian cancer on screening, 2 additional women in the MMS group and 10 additional women in the USS arm had surgery where the ovaries were only found to have benign lesions or were normal. The surgical complication rate of these additional operations was around 3

NO DECREASE IN MORTALITY SEEN YET

• Tests not sufficiently sensitive or specific
• High false positive rate (especially pre/peri-menopausal women)
• Unacceptable number of unnecessary surgeries
• No evidence of reduced mortality
CA125 only raised in 50-60% early stage disease and often normal in mucinous tumours
No national ovarian screening programme

OVARIAN SCREENING TRIAL (UKCTOCS): WHAT YOU NEED TO KNOW

Around 200,000 women aged 50-74 were split into 3 groups

**GROUP 1**
No screening

**GROUP 2**
Yearly blood test

**GROUP 3**
Yearly ultrasound

After 14 years, about 1,300 women had developed ovarian cancer of whom about 650 had died

Analysis suggests that, for every 10 women who died with no screening, 2 lives could have been saved with yearly blood tests

However, this figure is in the middle of a range. The actual number of lives saved could be anywhere between 0 and 4

So there may be no benefit at all

Or as many as four lives saved

And ovarian cancer screening also has risks

**HARMS CAN INCLUDE**

- Unnecessary surgery from false alarms
- Complications due to surgery
- Anxiety caused by screening and false alarms

The trial needs to continue for longer to collect more data so we can be more certain about benefits and harms

WE WILL BEAT CANCER SOONER
cr.uk.org
Ovarian cancer FIGO staging

Stage 1A
- Cancer in one ovary

Stage 1B
- Cancer in both ovaries

Stage 1C
- Cancer in the ovary and on the surface of one ovary

Stage 2A
- Peritoneal metastasis beyond pelvis (microscopic)

Stage 2B
- Cancer has spread to the bowel or bladder

Stage 2C
- Cancer cells also in the fluid of the abdomen

Stage 3A
- Peritoneal metastasis beyond pelvis
- Peritoneal metastasis 2cm or smaller

Stage 3B
- Peritoneal metastasis beyond pelvis
- Peritoneal metastasis 2cm or smaller

Stage 3C
- Peritoneal metastasis beyond pelvis
- Peritoneal metastasis >2cm or local lymph node metastasis

Stage 4
- Cancer has spread to other organs

Lymph nodes
- Ovary
- Womb

Bowel
An example of the course of advanced ovarian cancer

- Surgery and first-line chemotherapy
- TFI: 15 months
- Remission
- 2nd line chemotherapy: Etoposide and carboplatin with cisplatin
- 3rd line chemotherapy: Weekly paclitaxel
- 4th line chemotherapy: Bevacizumab
- Severe clots, bowel obstruction
- Death
Key principles:
treatment involves specialist teams, providing:
multi-disciplinary management:
surgery
chemotherapy
and
individualized care:
clinicians
nurse specialists

Aim of initial treatment: to obtain complete remission through surgery and chemotherapy
Standard management of ovarian cancer patients - Team work

- Gynaecological Oncologist
- Medical Oncologist
- Research team
- Palliative Team
- Histopathologist
- Cancer Nurses
- Primary Care Team
- Anaesthetist/I TU team
- Radiologist
- Plastic Surgeon
- Dieticians
- Clinical Oncologist
- Urologist
SURGERY IN OVARIAN CANCER

- **Roles include:**
  - diagnostic biopsy
  - therapeutic **optimal** debulking ie removal of all visible tumour
  - palliative relief of symptoms of bowel obstruction, etc

- **Issues include:**
  - timing primary or ‘interval’ surgery ie chemotherapy before or during
  - role of surgery in relapsed disease
INITIAL TREATMENT OF OVARIAN CANCER

Surgery
- Total abdominal hysterectomy (TAH)
- Bilateral salpingo-oophorectomy (BSO)
- Omentectomy
- Paraortic + pelvic lymphadenectomy
- Peritoneal Washings
- Residual disease 0, <1cm, >1cm

‘optimal or sub-optimal’

Chemotherapy
Carboplatin + paclitaxel x 6 (add in bevacizumab for high-risk)

initial or interval debulking
all patients are offered chemotherapy except women who have had optimal surgical staging and have low-risk stage I disease (grade 1 or 2, stage Ia or Ib)
The impact of residual tumour on outcome in advanced ovarian cancer
Data from an individual patient meta-analysis of three randomised phase III trials with 3,126 patients

5-year survival rate

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–10mm vs 0mm:</td>
</tr>
<tr>
<td>&gt;10mm vs 1–10mm:</td>
</tr>
</tbody>
</table>

log-rank: p<0.0001

Medical Disclaimer: The information presented here is for educational purposes only. It is not intended to replace professional medical advice, diagnosis, or treatment. Always consult your healthcare provider about any questions you may have regarding a medical condition. The content is not intended to be a substitute for professional medical advice, diagnosis, or treatment.


AIM NO RESIDUAL DISEASE
**OVARIAN CANCER - SURGERY NEW TECHNIQUES**

**Plasmajet**
- Device that generates argon plasma
- Ability to cut, ablate and coagulate disease with minimal collateral tissue damage
- Allows for usage on delicate structures; serosa and mesentery bowel

Royal Marsden Magazine
- In widespread small volume ovarian cancer obtain higher rate of complete cytoreduction
- Reduce bowel resections, stoma formation
- Cost reduction: stapling devices, post-operative stoma-care, reduced Length of stay
OVARIAN CANCER- FIRST LINE SYSTEMIC THERAPY
NEOADJUVANT (NACT)

**EORTC 55971**

- **NACT**
- **IDS**
- **Chemotherapy**

**Stage IIIc-IV Randomized**

- TC q3wks, 3 cycles
- IC q 3wks, 3 cycles

**Chemotherapy:**
- Platinum-based (cisplatin >75 mg/m² or carboplatin AUC 5)
- Fluorouracil (paclitaxel 175 mg/m² 3 hours of docetaxel 75 mg/m²)

**718 patients enrolled**

**EORTC/NCIC Study: NACT + Interval-OP**

**Overall survival**

**Recommendations:** All women with suspected stage IIIc or IV invasive epithelial ovarian cancer should be evaluated by a gynecologic oncologist prior to initiation of therapy. The primary clinical evaluation should include a CT of the abdomen and pelvis, and chest imaging (CT preferred). Women with a high perioperative risk profile or a low likelihood of achieving cytoreduction to <1 cm of residual disease (ideally to no visible disease) should receive neoadjuvant chemotherapy. Women who are fit for primary cytoreductive surgery, and with potentially resectable disease, may receive either neoadjuvant chemotherapy or primary cytoreductive surgery. However, primary cytoreductive surgery is preferred if there is a high likelihood of achieving cytoreduction to <1 cm (ideally to no visible disease) with acceptable morbidity. Before neoadjuvant chemotherapy is delivered, all patients should have confirmation of an invasive ovarian, fallopian tube, or peritoneal cancer.

Additional information is available at [www.asco.org/NACT-ovarian-guideline](http://www.asco.org/NACT-ovarian-guideline) and [www.asco.org/guidelineswiki](http://www.asco.org/guidelineswiki).

**Surgery after 3-4 cycles recommended**
OVARIAN CANCER - FIRST LINE SYSTEMIC THERAPY

- Standard of care - Carboplatin AUC5 in combination with paclitaxel 175mg/m² 3 wkly iv 6 cycles (ICON8 trial ESMO 2017) Initial or interval debulking

  **Even if poor performance status**

  Poor performance status (PS) is an indication for an aggressive approach to neoadjuvant chemotherapy in patients with advanced epithelial ovarian cancer (EOC)

- All patients are offered chemotherapy except women who have had optimal surgical staging and have low-risk stage I disease (grade 1 or 2, stage Ia or Ib)
  Role of chemotherapy in specific subtypes which are considered relatively chemoresistant questioned
  eg stage 1A clear cell, 1c mucinous, 1c low grade serous

  No prospective trials of adjuvant therapy in rare subsets of ovarian cancer
  Discuss role of chemotherapy with patients
POTENTIAL COMPLICATIONS AFTER OVARIAN DEBULKING SURGERY

UTI
Wound infection
Seroma/Wound Haematoma
Lymphocyst
Ileus
Pneumonia
Wound Dehiscence

Atrial Fibrillation
DVT/PE
Pancreatic fistula (post splenectomy)
Colovaginal fistula
Anastomotic leak
Ureteric fistula
Sub-phrenic abscess
OVARIAN CANCER-DRUGS

- Evolution over 50 years:
  - **1970** single agent cyclophosphamide was treatment of choice
  - **1975** first reports of activity of cisplatin in ovarian cancer
  - **1980’s** standard of care - cyclophosphamide/cisplatin
  - **1993** first approval of paclitaxel for treatment of ovarian cancer
  - **1996 – 2000** cisplatin/paclitaxel replaces cyclophosphamide as standard therapy
  - **2003** carboplatin/paclitaxel replaces cisplatin/paclitaxel as standard therapy
  - **2011** bevacizumab standard care in Europe
  - **2015** First biomarker directed treatment - BRCA PARP inhibitor olaparib maintenance
  - **2016, 2017** 3 PARP inhibitors licensed BRCA and beyond
  - **2019** 1st line PARP inhibitor
WHAT DOES INDIVIDUALISED TREATMENT MEAN?

Key factors in decision-making:

- disease stage (I – IV)
- pathology
  - high grade serous/papillary/endometrioid
  - mucinous
  - clear cell
  - low grade invasive
  - borderline
  - other, including stromas/carcinosarcoma
- patient factors
  - co-morbidity
  - renal function
  - age
TREATMENT OF RECURRENT OVARIAN CANCER

Issues:

- which treatment?
  - how long since previous chemo;
  - repeat platinum-based treatment if > 6 months
- further surgery?
  - consider if initial treatment achieved CR, recurrence at limited no. of sites and no ascites present
- when to start?
  - rising CA125 alone insufficient
  - key is presence of symptoms, CT scan changes
  - some clinicians consider CA125 monitoring unnecessary
Platinum-Free Interval and Efficacy - shorter interval, lower response

### Platinum-free Interval (months)

<table>
<thead>
<tr>
<th>Interval</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-12</td>
<td>27%</td>
</tr>
<tr>
<td>13-24</td>
<td>33%</td>
</tr>
<tr>
<td>&gt; 24</td>
<td>59%</td>
</tr>
</tbody>
</table>

**Markman et al 1991**

### Time to re-challenge

<table>
<thead>
<tr>
<th>Time</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>17%</td>
</tr>
<tr>
<td>1-2 years</td>
<td>27%</td>
</tr>
<tr>
<td>&gt; 2 years</td>
<td>57%</td>
</tr>
</tbody>
</table>

**Gore et al 1990**

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Pujade-Lauraine et al ASCO 2002
OVARIAN CANCER - TREATING RELAPSE

Too Early

Correct
PS 0 - 1

Too Late
PS 3 - 4

Serum CA125

CA 125↑

= RECURRENT OVARIAN CANCER

= INCURABLE CANCER

= PALLIATIVE TREATMENT

Gore 2001, ASCO Education Book
Recurrent Ovarian Cancer- Options

Traditional definitions to guide therapy and for majority of clinical trials

- **Platinum resistant**
  - <6 months
    - wkly paclitaxel, PLD, topotecan, gemcitabine, carboplatin with gemcitabine, hormonal therapy
    - Palliative care

- **Partially platinum-sensitive**
  - 6-12 months
    - Carboplatin combination (PLD, gemcitabine or paclitaxel)
    - nonplatinum (PLD+/- trabectedin)

- **platinum-sensitive**
  - >6 months
    - Carboplatin combination (PLD, gemcitabine, gem+bevacizumab or paclitaxel)
    - Surgery?
    - Maintenance bevacizumab
    - Maintenance olaparib

Clinical Trials
Bowel Obstruction/Palliative Surgery – individualised management

Courtesy of John Butler
PALLIATIVE SURGERY

1. Is the surgery technically feasible?
2. Is the patient fit, both physically and emotionally, for surgery and recovery?
3. Is the patient likely to benefit from the surgery?
   (tolerate oral feeding at discharge/ the ability to resume a normal diet)
TOXICITES RELATED TO CHEMOTHERAPY

– Myelosuppression
– Neutropenic sepsis
– Nausea and vomiting
– Fatigue
– Loss of appetite
– Hair loss
– Hand and foot rashes
– Renal toxicity
– Peripheral neuropathy
– Mouth sores
– Allergy
– Diarrhoea
Which toxicities to be aware of for patients receiving chemotherapy?

- **Myelosuppression**
  - **Neutropenic sepsis**
    
    Temperature $\geq 38.5^\circ$ C or 2 readings $\geq 38^\circ$ C and an absolute neutrophil count of $\leq 0.5 \times 10^9$/L
    
    URGENT hospital admission and iv antibiotics (< 1 hour door to needle time)

- nausea and vomiting
- fatigue
- loss of appetite
- hair loss (not all chemotherapy causes hair loss, scalp cooling may be useful for some regimens)
- hand and foot rashes
- Renal toxicity
- Peripheral neuropathy
- mouth sores
- Allergy
- Diarrhoea

*Contact oncology team if unsure about a symptom or severe*
The treatment of ovarian cancer is undergoing rapid changes....

immunotherapy
I read that this latest treatment can help treat my cancer—can I have it doctor?

A 'wonder drug' that could kill ALL types of cancer

By FIONA MACRAE
UPDATED: 08:00, 27 June 2011

Ovarian cancer discovery gives hope to women after biggest breakthrough in two decades

By MAIL ON SUNDAY REPORTER
UPDATED: 01:44, 5 June 2011

Comments (3) Share 0 Tweet 11 Like 115

A drug has been hailed as the biggest breakthrough in 20 years of ovarian cancer research after trials showed it can increase patients' life expectancy by up to eight months.

British researchers found Avastin, which is used to treat breast and bowel cancers, is also effective against ovarian cancer.

The disease has been called the 'silent killer' because it often has no symptoms in the early stages and in 80 per cent of cases is not detected until it has spread.

'Major breakthrough' for hundreds of women with incurable ovarian cancer as NHS approves a 'milestone' pill that halts the spread of the disease

- A drug which halts the spread of ovarian cancer is now available to NHS patients
- Drug rationing chiefs gave the green light for the pill called niraparib
- Charities hailed the change as a 'major breakthrough' for thousands of women
- Treatment can freeze tumours for months at a time and helps prevent relapses
- Ovarian cancer affects about 7,400 people in the UK every year, killing 4,100

By KATE PICKLES HEALTH REPORTER FOR THE DAILY MAIL
PUBLISHED: 08:46, 1 June 2018 | UPDATED: 14:11, 1 June 2018
First-line bevacizumab for ovarian cancer—new standard of care?

Susana Banerjee and Stan B. Kaye

Bevacizumab (Avastin)
Monoclonal antibody against VEGF

Antiangiogenic agent

Used in colorectal, renal cancers

Toxicities:
- Hypertension
- Proteinuria
- Bleeding
- Perforation
- Thrombosis- arterial and venous

License also in recurrent disease
Bevacizumab (Avastin) increases survival in Ovarian and Cervical Cancer

News and Views

Nature Reviews Clinical Oncology 9, 194-196 (April 2012) | doi:10.1038/nrclinonc.2012.28

Gynecological cancer: First-line bevacizumab for ovarian cancer—new standard of care?

Susana Banerjee & Stan B. Kaye

Bevacizumab in Combination with Carboplatin/paclitaxel followed by maintenance prolongs progression-free Survival and overall survival in High-risk patients


Bevacizumab in cervical cancer: a step forward for survival.

Banerjee S1. Median overall survival 13.3 to 16.8 months
First-line bevacizumab for ovarian cancer—new standard of care?

Susana Banerjee and Stan B. Kaye

GOG218 PFS extended by 3.8 months (14.1 months versus 10.3 months; HR $P < 0.001$)

ICON7-high-risk group overall survival (28.8 vs 36.6 months; HR = 0.64, $P = 0.002$)

Bevacizumab in Combination with Carboplatin/paclitaxel followed by maintenance prolongs progression-free survival and overall survival in high-risk patients

**ICON7 NEJM 2011**
BRCA1 AND BRCA2 OVARIAN CANCER

Around 17% of ovarian cancer patients are BRCA1/2 germline mutation positive\(^1,2\)

- 23% <50 had a mutation vs 12% >50 yrs

Over 40% of BRCA germline positive women with ovarian cancer had no family history of ovarian/breast cancer\(^1\)

5 year survival BRCA1 44% BRCA2 61% no mutation 25%
HOW DOES BRCA MUTATION STATUS OF MY PATIENT WITH OVARIAN CANCER IMPACT ON MANAGEMENT?

1. Information on clinical outcome and prognosis
   better survival, higher response to chemotherapy
   Associated with visceral metastases (liver, spleen, brain, lung)

2. Treatment options:
   - Offer BRCA1/2 mutation carriers a PARP inhibitors
   - Treatment scheduling: clinicians are more likely to pursue rechallenging BRCA carriers with platinum-based chemotherapy. Evidence that BRCA carriers may be more sensitive to anthracylines
   - Identify and appropriately counsel patients with ovarian cancer that are also at risk of other BRCA-associated cancers eg. Breast

3. Identify family members at risk of BRCA related cancers
Mechanism of synthetic lethality between BRCA deficiency and PARP inhibition

DNA damage → Repair of SSB by Base Excision Repair → PARP inhibition

Formation of single strand DNA break (SSB)

Repair of SSB by Base Excision Repair

PARP inhibition

Impairs base excision repair

SSB persists

DNA replication: Replication fork arrests at SSB

Formation of double strand breaks (DSBs) or replication fork collapse

Normal cell with functional HR pathway

HR-deficient tumour cell (BRCA deficient)

CELL SURVIVAL

Impaired HR-mediated DNA repair

CELL DEATH

TUMOUR-SELECTIVE CELL DEATH (Synthetic Lethality)

Banerjee, Kaye and Ashworth (2010)
PARP inhibitors - Rationale for practice-changing studies

Around 50% of high grade serous OC could benefit from PARP inhibitors

Clear evidence of beneficial tumour response in heavily pretreated cancer patients with BRCA mutations

Fong et al JCO 2010

Audeh et al Lancet 2010

The clinical implications of a BRCA mutation in ovarian cancer

Delivering widespread BRCA testing and PARP inhibition to patients with ovarian cancer

*Nat Rev Clin Onc 2017*

Angela George¹, Stan Kaye² and Susana Banerjee²

**PARP inhibitors effective: predictor of PARP inhibitor sensitivity**

**Olaparib-phase III (SOLO2)**

Hazard Ratio 0.30 (95% CI 0.22-0.41)

P<0.0001

**Niraparib-phase III (NOVA)**

Hazard Ratio 0.27 (95% CI 0.17-0.41)

P<0.001

**PARP inhibitors are approved in ovarian cancer**

Olaparib maintenance therapy high grade regardless of BRCA status

Niraparib maintenance therapy high grade serous regardless of BRCA status

Rucaparib treatment for relapsed disease BRCA mutated
PARP inhibitors – monumental, practice-changing progress over the last few years in ovarian cancer

Study 19

ENGOT-OV16/NOVA TRIAL

Dec 2014 EMA olaparib capsules for maintenance BRCA mutated
Dec 2014 FDA olaparib capsules treatment gBRCA ovarian cancer more than 3 prior
2016 FDA rucaparib treatment BRCA mutated 2 or more prior lines
2017 FDA niraparib for maintenance (regardless of BRCA/HRD status)
2017 FDA olaparib tablets maintenance (regardless of BRCA/HRD status)
olaparib tablets for treatment gBRCA
2017 EMA niraparib for maintenance (regardless of BRCA/HRD status)
2018 EMA olaparib tablets maintenance (regardless of BRCA/HRD status)
2018 FDA rucaparib maintenance (regardless of BRCA/HRD status)
2018 EMA rucaparib maintenance (regardless of BRCA/HRD status)
2018 FDA rucaparib treatment BRCA mutated 2 or more prior lines
2018 FDA olaparib maintenance 1st line
2019 EMA olaparib maintenance 1st line
THE UNMET NEED IN OVARIAN CANCER

- ~250,000 cases/year worldwide\(^1\)
- Platinum-based chemotherapy
- Bevacizumab
- 10-18 months Median progression-free survival\(^2,3,4\)
- 70%–80% of women relapse within 2 years of frontline treatment\(^2,3\)
- 30%–40% 5-year survival rate\(^1\)

There is a significant need for better frontline treatment to improve outcomes for women with ovarian cancer

SOLO-1: PHASE III TRIAL OF MAINTENANCE OLAPARIB FOLLOWING PLATINUM-BASED CHEMOTHERAPY IN NEWLY DIAGNOSED PATIENTS WITH ADVANCED OVARIAN CANCER AND A BRCA1/2 MUTATION

Kathleen Moore,1 Nicoletta Colombo,2 Giovanni Scambia,3 Byoung-Gie Kim,4 Ana Oaknin,5 Michael Friedlander,6 Alla Lisianskaya,7 Anne Floquet,8 Alexandra Leary,9 Gabe S. Sonke,10 Charlie Gourley,11 Susana Banerjee,12 Amit Oza,13 Antonio González-Martín,14 Carol Aghajanian,15 William Bradley,16 Elizabeth S. Lowe,17 Ralph Bloomfield,18 Paul DiSilvestro19

1Stephenson Oklahoma Cancer Center, Oklahoma City, OK, USA; 2University of Milan-Bicocca and IEO, European Institute of Oncology IRCCS, Milan, Italy; 3Fondazione Policlinico Universitario A. Gemelli IRCCS Università Cattolica, Rome, Italy; 4Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; 5Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; 6University of New South Wales Clinical School, Prince of Wales Hospital, Randwick, Australia; 7St Petersburg City Oncology Dispensary, St Petersburg, Russia; 8Institut Bergonié, Comprehensive Cancer Centre, Bordeaux, France; 9Gustave-Roussy Cancer Campus, Villejuif, France; 10The Netherlands Cancer Institute, Amsterdam, The Netherlands; 11Cancer Research UK Edinburgh Centre, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK; 12The Royal Marsden NHS Foundation Trust, London, UK; 13Princess Margaret Cancer Centre, Toronto, ON, Canada; 14IMD Anderson Cancer Centre Madrid, Madrid, Spain; 15Memorial Sloan Kettering Cancer Center, New York, NY, USA; 16Froedtert and the Medical College of Wisconsin, Milwaukee, WI, USA; 17AstraZeneca, Gaihensburg, MD, USA; 18AstraZeneca, Cambridge, UK; 19Women & Infants Hospital, Providence, RI, USA

ClinicalTrials.gov identifier: NCT01844986. This study was sponsored by AstraZeneca; part of an alliance between AstraZeneca and Merck & Co., Inc.
SOLO-1: Study Design

- Newly diagnosed, FIGO stage III-IV, high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer and/or fallopian tube cancer
- Germline or somatic BRCAm
- ECOG performance status 0-1
- Cytoreductive surgery
- Completed platinum-based chemotherapy
- In clinical complete response or partial response

```
Olaparib 300 mg BID (n=260)

2:1 randomisation
Stratified by response to platinum-based chemotherapy
```

```
Placebo (n=131)
```

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

```
Primary endpoint
Investigator-assessed PFS (modified RECIST 1.1)
```

```
Secondary endpoints
PFS using BICR
PF52
Overall survival
Time from randomisation to first subsequent therapy or death
Time from randomisation to second subsequent therapy or death
HRQoL (FACT-O TOI score)
```

BICR = blinded independent central review; BID = twice daily; ECOG = Eastern Cooperative Oncology Group; FACT-O = Functional Assessment of Cancer Therapy – Ovarian Cancer; FIGO = International Federation of Gynecology and Obstetrics; HRQoL = health-related quality of life; PFS = progression-free survival; PF52 = time to second progression or death; RECIST = Response Evaluation Criteria in Solid Tumours; TOI = Trial Outcome Index.
Moore K et al. Presented at: ESMO annual meeting; 2018.
PFS by investigator assessment

- 60.4% progression free at 3 years
- 26.9% progression free at 3 years

Events (%) [50.6% maturity]

Medians PFS, months 

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<th>Placebo (N=131)</th>
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<td>102 (39.2)</td>
<td>96 (73.3)</td>
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HR 0.30

95% CI 0.23, 0.41; P<0.0001

No. at risk

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<td>260</td>
<td>131</td>
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Months since randomization

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<th>Placebo</th>
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<tr>
<td>201 194</td>
<td>184 172 149 138 133 111 88 45 36 4 3 0 0 0 0</td>
</tr>
<tr>
<td>221 212</td>
<td>220 212 211 194 184 172 149 138 133 111 88 45 36 4 3 0 0 0 0</td>
</tr>
</tbody>
</table>

Moore et al NEJM 2018

CI, confidence interval; NR, not reached
CLINICAL CONSIDERATIONS FOR DISCUSSION: MANAGING ADVERSE EVENTS FOR PATIENTS ON OLAPARIB

Maintaining patients on treatment in the first 3 months is imperative to treatment success as this is often a difficult time for patients, appropriate AE management strategies can help to achieve this.¹,²

Fatigue (very common*)
• Encourage exercise
• May require dose reduction/interruption

Anaemia (very common)
• Check iron levels
• Transfuse as required
• May require dose reduction/interruption

Nausea (very common)
• Antiemetics such as prokinetics or H1-receptor antagonists
  • E.g. domperidone 10mg oral tablets, up to 3x a day, or as required
  • May require dose reduction/interruption

Diarrhoea (very common)
• Conservative measures
• Anti-diarrheal agents
• May require dose reduction
• May require dose reduction/interruption

* A 'very common' (all CTCAE grades) frequency indicates that approximately ≥ 1/10 patients will be affected

### Genetic testing in oncology clinics: Royal Marsden Ovarian cancer BRCA testing model

#### Obtaining consent
- Medical testing carried out through trained “consent to BRCA testing” cancer team
- All testing in non-diagnosed patients done through Genetics

#### Interpreting results
- Interpreted by geneticists so clear information is returned

#### Sharing results
- Negative tests valuable but unlikely to require Genetic follow-up; cancer team share results with patient
- Positive tests result in a Genetics appointment

---

Genetic testing in oncology clinics:
Initial Study Royal Marsden: July 2013 - Jan 2015

Delivering widespread BRCA testing and PARP inhibition to patients with ovarian cancer

207 patients with non-mucinous ovarian cancer tested (first line, relapse, follow-up)

Oncologists explained the test and secured patients’ consent, usually during the first consultation

All 207 women took up the offer of a test

All patients thought they had been given sufficient information on which to base their decision to undergo the test - no patients referred to genetics for extra discussion

RMH/ICR have made consent training for oncologists available as online modules
Training is available at:
http://mcgprogramme.com/brcatesting/

33 patients (16%) germline BRCA mutation
>50% no family/personal history and would not have been tested under previous criteria

None of the patients who tested positive reported undue distress in informing their relatives about the risk

Turn around time < 4 weeks

Acknowledgements

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NIHR RM/ICR Biomedical Research Centre

The ROYAL MARSDEN

ICR The Institute of Cancer Research