New Directions in Treatment of Ovarian Cancer

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Newly diagnosed: scenario

Ist line
- Surgery
- chemotherapy

Cure
If can’t cure – can we turn into chronic disease?

1st line

2nd line

3rd line
BRCA  
Histology  
Genomic Signature

Patient group

Drug toxic but beneficial

Drug NOT toxic and NOT beneficial

Same diagnosis, same prescription

Drug toxic but NOT beneficial

Drug NOT toxic and beneficial
Ovarian Cancer

• **Approach** - understand the biology
  – Its not one disease
  – Origins - fallopian, GI, endometriosis
  – “Seed, soil and nourishment”

• **Improve precision of diagnosis and treatment**
• Define populations and treat according to profile
• Determine activity which is clinically meaningful
  – Appropriate control for reference
• Characterize responders and resistant patients
Personalized therapy or precision therapy

Current targeting activities

- Pathology based trials
  - Define population - but control may also fare better
- Activation pathways
- Homologous Recombination deficiency
- P53 mutations
- Receptor targeting
- Immunotherapy

Challenges

- Genomic instability and chaos
- Heterogeneity: temporal and spatial
- Resistance and sensitivity
- Macro-environment
Targeted therapies in ovarian cancer.


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Histologic subtypes of epithelial ovarian carcinoma and associated mutations/molecular aberrations. *, CHK2, BARD1, BRIP1, PALB2, RAD50, RAD51C, ATM, ATR, EMSY, Fanconi anemia genes.

Clinical Trials

- The rigorous testing to safely assess toxicity and activity of new treatments
- To compare new therapies with established to show if improve outcomes
  - Do women live longer
  - Do they have a longer period of time without disease
  - Do they feel better and have better quality of life
  - How safe is it – risk vs benefit?
Conducting a clinical trial

• Protocol
• Has to be approved by Health Canada, Hospital
• Has to have independent approval from an ethics board
• Risks and benefits explained clearly to patients
• Has to be conducted to Good Clinical Practice standards
  – Protocol has to be followed exactly
  – Side effects and activity measured accurately and promptly
How does a new drug get approved for use in Canada?

How long?
Strength of the evidence?
Restrictions on use?
• Improve our understanding of biology.
• Design the right studies.
• Individualize therapy.
• Measure improvement in outcomes that make sense
Why we do trials at PMH

- To improve treatment and outcome: Cure and Control
- Offer new therapies to patients
- To learn how best to introduce new treatment
- Carefully assess risks and benefits
  - Close monitoring in early stages
  - Make sure risks are minimized
  - Learn how to manage side effects
  - Communicate with peers internationally
Whats new, what's hot – but don’t forget the tried and tested...

- Anti-angiogenics – first line, second line
- Parp and DNA repair inhibitors
- Improving drug delivery – precision bombing
- Disrupting cancer cell’s internal machinery for messaging and growth
- Immune approaches
- Using viruses against the cancer
- Combinations of the above
So what approaches can we take?

• Modulate the micro-environment
• Leverage potential for synthetic lethality
• Target driver mutations.
• Exploit unique expression on cells
• Immunologic approaches
• Remember the macro-environment.
Treatment modalities

- Surgery
- Chemotherapy

Diagram:

- Left: Surgery → Chemotherapy → Surgery
- Right: Surgery → Chemotherapy → Surgery
Chemotherapy after surgery

- Any disease visible?
- Is there a role for intraperitoneal chemotherapy?
- What type of iv chemotherapy?
- Every 3 weeks or weekly?
- New drugs?
Improving personalization and precision in ovarian cancer

- Understanding genetic susceptibility: BRCA
- Use available treatments more effectively
- Use new treatments
New agents in maintenance

Anti-angiogenics

• Bevacizumab
  – Concurrent with chemotherapy and continue beyond chemotherapy in first line
  – Delays recurrence
  – Improves survival in women at high risk
  – 5-9 months on average

• Pazopanib
  – Start after chemotherapy
  – Delays recurrence

Parp inhibitors

• Delay recurrence if given post chemotherapy
• Effect greatest in women with BRCA mutations
• Oral, generally well tolerated
• Several trials for women with and without BRCA mutations
  – First line
  – Second/subsequent line platinum sensitive
• Ovarian cancer secretes protein to control blood vessel growth
• This protein makes vessels leaky – ascites
• Can be targeted in many ways
Anti-angiogenic treatment

3 initial studies in 150 women

5 studies in 5000 women
Anti-angiogenics

Bevacizumab

- 4 RP3 studies – positive
- Outcome related to disease burden
- Duration of therapy?
- When to initiate bevacizumab?
- Bev – combinations

- Approval in Europe
  - First line
  - Second line sensitive

- PFS
- OS in high risk

ICON7

- PFS
- Not OS

Oceans

- PFS
- Crossover Design

Aurelia

- PFS
- Approval in Europe
  - First line
  - Second line sensitive
Anti-Angiogenics

**Bevacizumab**
4 RP3 studies – positive
Duration of therapy?
When to initiate bevacizumab?
Bev – combinations

**Pazopanib**
AGO-Ovar 16

**Trebananib – AMG386**
Trinova 1 – ECCO 2013
Bevacizumab (Avastin)

First Line
- Delays recurrence
- Improves survival in women at highest risk

Second Line
- With chemotherapy
- Delays recurrence of disease

In resistant recurrence
- With chemotherapy
- Delays recurrence
- May improve survival in some settings
Parp Inhibitors: Olaparib, Niraparib, Veliparib, Rucaparib

- Oral pills/capsules
- Well tolerated, manageable side effects
- Active in women with BRCA mutations
- **Active in women with high grade serous cancers (PMH)**
- How should drug best be incorporated in therapy
  - With chemo?
  - On its own following chemotherapy?
  - Which groups of women?
Strong family history

Ovarian BRCA1−/−
So what approaches can we take? Exploiting unique expression on cells.

- Target driver mutations.
- Modulate the micro-environment.
- Leverage potential for synthetic lethality.
- Exploit unique expression on cells.
- Immunologic approaches.
- Remember the macro-environment.

FR antibody conjugated with chemotherapy loaded with porphysomes.

FR tagged porphysomes.
Folate Receptor Expression

% Cases FR Positive

- Ovarian
- Colorectal
- Endometrial
- Breast
- Pancreatic
- Stomach
- Gallbladder
- Liver
- Kidney
- Prostate
- Testicular
- Bladder
- Head and Neck

pmol FR/ mg protein

Stage I
Stage II
Stage III
Stage IV
Folate receptor targeting: Endocyte Trial

Platinum resistant ovarian cancer patients (failed first or second platinum therapy < 6 months)

- Receptor Scan

EC145 + Doxil®
2.5mg TIW wks 1, 3

Doxil® only
50 mg/m² (IBW) every 28 days

n = 640 patients
Adoptive T cell Therapy

- Tumor excision
- Expand Cells
- Transfer into treated patients ($10^{10} - 10^{11}$ cells)
- High-dose IL-2
- Test T cell specificity
- Culture T cells

30-70 % objective response
22% complete responders

Dudley et al
Science (2002) 298; 850
J Clin Oncol (2005) 22;2346
J Clin Oncol (2008) 26;5233


Pam Ohashi
Initiation and Progression of HGS
Bowtell: 2010

- Genomic instability
  - Associated with improved outcome
- Aneuploidy: common in OC
- High expression of PLK4
  - Centrosome/centriole duplication and segregation
- PLK4 inhibitor: CFI400945
Circulating DNA
Murtaza, Rosenfeld, Brenton et al.

Figure 1: Identification of treatment-associated mutational changes from exome sequencing of serial plasma samples.

Overview of the study design: plasma was collected before treatment and at multiple time-points during treatment and follow-up of advanced cancer patients. Exome sequencing was performed on circulating DNA from plasma at selecte...