How to fight a silent killer: Lessons learned from Ovarian Cancer

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• Ovarian cancer is not common but is highly lethal
• Most patients present with extensive tumor spread that is difficult to cure
• Can often achieve remission, but microscopic amounts of cancer escape chemotherapy and eventually grow back to cause relapse
• Such relapses are often difficult to control due to the development of chemotherapy resistance
Typical course of ovarian cancer

1. Diagnosis
2. Surgery
3. Chemotherapy
4. Remission, but *hidden microscopic residual cancer*
5. More chemotherapy that eventually doesn’t work due to *resistance*
6. Clinical relapse

*Twice the Knowledge*

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Typical course of ovarian cancer

Need better initial treatment

Diagnosis

Surgery

Chemotherapy

Remission, but hidden microscopic residual cancer

More chemotherapy that eventually doesn’t work due to resistance

Clinical relapse
Taxus Brevifolia

Paclitaxel (Taxol)
Survival
By Treatment Group

Proportion Surviving

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

Rx Group

Alive  Dead  Total
IV     93     117   210
IP     117    88    205

Months on Study

Proportion Surviving

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

0 12 24 36 48 60

Rx Group

IV
IP
Somatic mutation → Small avascular tumor → Proangiogenic factors secreted by tumors and nearby stromal cells stimulate angiogenesis → Tumor vascularization allows rapid tumor growth and metastasis

Targeting VEGF

Ovarian Cancer Cell

VEGF-A

Blood Vessel Cell

Bevacizumab

VEGF R-2
(KDR/flk-1)

ANGIOGENESIS
VASCULOGENESIS

T W I C E  T H E  K N O W L E D G E
twicethetrust.org
Phase II Study of Bevacizumab in Patients With Platinum-Resistant Ovarian Cancer or Peritoneal Serous Cancer


**GOG218: Ovarian (stage III-IV)**

- Epithelial Ovarian or Primary Peritoneal Cancer
- Suboptimal Cytoreduction
- Collaborative design (GOG, NCI, Genentech)

### Protocol Details

**I**
- Paclitaxel 175 mg/m² (3 h)
- Carboplatin AUC=6.0
- Placebo q21d*
- x 6
- Placebo (14 m total)

**II**
- Paclitaxel 175 mg/m² (3 h)
- Carboplatin AUC=6.0
- Bevacizumab 15 mg/kg q21d*
- x 6
- Placebo (14 m total)

**III**
- Paclitaxel 175 mg/m² (3 h)
- Carboplatin AUC=6.0
- Bevacizumab 15 mg/kg q21d*
- x 6
- Bevacizumab (14 m total)

*starting with C2

Open: Sep-05
Closed: ---
Target Accrual: 2000 pts (3 Y)

Burger, et al.
Typical course of ovarian cancer

taxanes, IP therapy, bevacizumab, but what about drug resistance?

Diagnosis

Surgery

Chemotherapy

Remission, but *hidden microscopic residual cancer*

Clinical relapse

More chemotherapy that eventually doesn’t work due to resistance
GENE CHIP- the key to understanding mechanisms of drug resistance
Association between the Ovarian Cancer Prognostic Profile (OCPP) and overall survival

A

Number at risk:
Unfavorable profile 18 17 14 7 6 3 2 1 0
Favorable profile 16 15 15 14 11 5 2 0 0

B

Number at risk:
Unfavorable profile 37 34 28 20 13 7 3 1 0
Favorable profile 31 30 30 27 21 12 6 1 0
Chemo Response Profile (CRP)

Resistant Sensitive

Genetic Pathway Identification

Functional Analysis

Gene Transfection  Gene Knock down  Mutational Analysis  Protein Expression

Novel drug target
Typical course of ovarian cancer

Need better ways to control residual tumor

Diagnosis

Surgery

Chemotherapy

Remission, but *hidden microscopic residual cancer*

More chemotherapy that eventually doesn't work due to *resistance*

Clinical relapse
Antigen Presentation

 Activation

 TCR
 MHC I or II
 CD28
 CD80, 86
 LFA-1
 ICAM-1
 CD2
 LFA-3
 CD40L
 CD40
 Dendritic cell

 IL-12

 Anergy

 TCR
 MHC I or II
 CD28
 LFA-1
 CD2
 CD40L
 Tumor cell
Adherent PBMCs cultured for 5-7 days with GM-CSF & IL-4; TNF-\(\alpha\) added for 48-72 hours

Tumor cells isolated

DCs assessed for DC & tumor specific markers

Tumor cells assessed for tumor & DC specific markers

DC & tumor fused with 50% PEG at DC: tumor, 3:1 to 10:1

Fusion cells quantified by measuring dual expression of unique DC & tumor markers

Doses prepared & frozen

Microbiology testing sent

Leukapharesis

Adherent PBMCs cultured for 5-7 days with GM-CSF & IL-4; TNF-\(\alpha\) added for 48-72 hours

DCs pulsed with KLH for control vaccine

CA125, MUC1, CD86, CD40, CD80, CD83

CD86, CA125, MUC1, CAM, DR

TWICE THE KNOWLEDGE
twicethetrust.org
Typical course of ovarian cancer

Vaccinate with tumor-dendritic cell fusion

Diagnosis

Surgery

Chemotherapy

Remission, but hidden microscopic residual cancer

Delay or prevent relapse?
Typical course of ovarian cancer

Need better treatment for disease relapse

Diagnosis

Surgery

Chemotherapy

Remission, but hidden microscopic residual cancer

More chemotherapy that eventually doesn’t work due to resistance

Clinical relapse