

# Epithelial Ovarian Cancer



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# Epithelial Ovarian Cancer



# Radiotherapy

## Ovarian Cancer



# Radiotherapy

- Ovarian cancer is usually radiosensitive
- Whole abdominal (WAR)
  - Microscopic disease
  - 2500-3000 cGy over 4-5 weeks
- Tumoricidal dose
  - > 2cm                      5000-6000 cGy
  - 0.5-2 cm                    4500-5000 cGy
  - Microscopic                2500-3000 cGy
- P-32 is radioactive chromium phosphate
  - IP colloid radiotherapy, beta emitter
  - T<sup>1/2</sup> 14.2 days
  - Toxicity

# Radiotherapy

## Limitations

- Extent and timing of disease often unknown
- Free mobility of cancer cells in abdomen
- Dose restrictions
  - Small intestine
  - Kidneys
  - Bone marrow
  - Adhesive peritonitis
- Not recommended for initial adjuvant treatment by NCCN

The price of anything  
is the amount of life you  
exchange for it

~Henry David Thoreau

# Chemotherapy

## General Considerations

Ovarian Cancer



# Chemotherapy

- Platinum-era changed the management of ovarian cancer
- Now Platinum/Taxane era
  - Carbo/Taxol are synergistic with no known biological explanation
  - Platelet-sparing effect
  - Improved survival
- Questions?
  - Route of administration
  - Dosing
  - Timing

# Chemotherapy

- It is unlikely that *new* cytotoxic agents, or new combinations of known agents, will have a lasting, favorable impact on the survival of advanced ovarian cancer.
- Is targeted therapy with biological agents the next frontier?

# Dose Intensity

- DI regimens remain investigational
- GOG 97
  - Cisplatin/Cytosin
  - 4 vs. 8 cycles, equivalent dose
  - No difference in progression-free or overall survival
- Colombo, 1993
  - Weekly Cisplatin 50 mg/m<sup>2</sup> for 9 weeks
  - Cisplatin 75 mg/m<sup>2</sup> q 3 wks for 6 cycles
  - No overall difference in progression-free or overall survival

# DI-No Benefit

| Trial      | Platinum dose                            | RR | Survival |
|------------|--|----|----------|
| GOG        | weekly Cisplatin                         | 65 | 21 mo    |
|            | 16.7 v. 33.3 mg/m <sup>2</sup>           | 59 | 24 mo    |
| GICOG      | weekly Cisplatin                         | 61 | 33 mo    |
|            | 25 v. 50 mg/m <sup>2</sup>               | 66 | 36 mo    |
| GONO       | weekly Cisplatin                         | 61 | 24 mo    |
|            | 12.5 v. 25 mg/m <sup>2</sup>             | 58 | 29 mo    |
| London GOG | Monthly Carbo                            | 57 | HR 0.91  |
|            | AUC 6 v. 12                              | 63 |          |
| Austrian   | Weekly Cis 25 mg/m <sup>2</sup>          | 42 | 38 mo    |
|            | Cis 25 mg/m <sup>2</sup> /wk <u>plus</u> | 39 | 42 mo    |
|            | Carbo 75mg/m <sup>2</sup> /wk            |    |          |

# DI-Benefit

| Trial     | Platinum dose                  | RR | Survival   |
|-----------|--------------------------------|----|------------|
| Scottish  | weekly Cisplatin               | 34 | 27%        |
|           | 16.7 v. 33.3 mg/m <sup>2</sup> | 61 | 32% @ 4yr  |
| Hong Kong | weekly Cisplatin               | 30 | 33%        |
|           | 20 v. 40 mg/m <sup>2</sup>     | 55 | 36% @ 3 yr |

# Bone Marrow Transplantation

- Investigational, dose-intense strategy
- Reported for several solid tumor types
- High dose chemo with autologous BMT
  - Improved response rates
  - Improved progression-free intervals
  - No overall survival advantage reported
- Toxicity concerns

# Biological Agents

- Herceptin
  - Mab against Her2-neu
- Ovarex
  - Mab against CA-125
- Erbitux
  - Mab against sEGFR
- Avastin
  - Mab against VEGF
- Gleevec
  - Tyrosine kinase inhibitor
- Iressa
  - EGFR tk inhibitor
- Fenretinide
  - Retinoid
- Velcade
  - Proteasome inhibitor

# Chemotherapy

## More Trials & Tribulations

Ovarian Cancer



# Chemotherapy

## GOG 111

- Cisplatin/Taxol improves overall survival versus Cisplatin/Cytosoxan.
  - Median survival
    - P/T 38 months
    - P/C 24 months
  - HR 0.61 in favor of P/T

McGuire, 1996

# Chemotherapy

## ICON2

- International Collaborative Ovarian Neoplasm, 1998
  - N=1526 patients
  - Carboplatin vs CAP
  - No survival difference

# Chemotherapy Trials

- GOG 158
  - Arm I: Cisplatin/Taxol
    - 75 mg/m<sup>2</sup> + 135 mg/m<sup>2</sup> over 24 hrs
  - Arm II: Carboplatin/Taxol
    - AUC 7.5 + 175 mg/m<sup>2</sup> over 3 hrs
  - Carbo/Taxol
    - Less toxic
    - Easier to administrate
    - Equal efficacy

# Chemotherapy Trials

- SCOTROC trial
  - Carbo/Taxol and Carbo/Taxotere
  - Taxotere 75 mg/m<sup>2</sup>
  - Neurotoxicity (30% v 10%)
  - Febrile neutropenia with Taxotere
  - Equal efficacy

# Chemotherapy Trials

- GOG 132
  - Cisplatin/Taxol is better than single agent Cisplatin or Taxol in higher doses
- GOG 134
  - Doubling of GCSF doesn't reduce febrile neutropenia associated with high dose Taxol
- GOG 178
  - Consolidation chemotherapy
  - Randomized to 3 vs. 12 months Taxol
  - Progression-free survival advantage and toxicity

# Chemotherapy

## GOG 172

- Following optimal cytoreduction
- Regimen
  - Day 1: Taxol 135 mg/m<sup>2</sup> IV over 24 hrs
  - Day 2: Cisplatin 100 mg/m<sup>2</sup> IP
  - Day 8: Taxol 60 mg/m<sup>2</sup> (max BSA 2.0)

# Chemotherapy

## GOG 172

- IP chemotherapy
  - Cisplatin and Taxol
  - Both IV and IP
  - Dose intensive and labor intensive
- Survival increased by 16 months
  - 65.6 vs. 49.7 months,  $p = 0.03$
- 42% completed regimen
  - Pain, leukopenia, catheter issues, infection

# Chemotherapy Intraperitoneal

- NCI clinical announcement, 2006
  - Eight phase III clinical trials
- Recommend IV with IP chemotherapy
  - Higher doses
  - More frequent infusions
- NCCN
  - *Alternative* to primary therapy

# Chemotherapy Intraperitoneal

- Only 42% completed 6 cycle treatment
- Leukopenia
- Infection
- Catheter complications
- Abdominal pain
- Fatigue
- Nausea/vomiting/  
dehydration

# Chemotherapy Intraperitoneal

- Not recommended when:
  - Poor performance status
  - Medical comorbidities
  - Advanced age
  - Stage IV or any extra-abdominal disease

# Chemotherapy Early Stage

Ovarian Cancer



# Early Ovarian Cancer Stage I

- Observation for Stage IA or IB grade 1 ovarian cancers
  - Young et al. NEJM, 1990
- If observation considered for grade 2 stage IA or IB, comprehensive surgical staging is strongly recommended

# Early Ovarian Cancer Stage I

- Low risk
  - No further therapy
    - Grade 1 and diploid
- High risk
  - Adjuvant chemotherapy
    - Aneuploid
    - Grade 2,3
    - Clear cell

# Early Ovarian Cancer Stage II

- 50% relapse and death
- GOG 175 closed, maturing
- Duration?
  - 3 vs. 6 cycles
- Single agent or combination

# Chemotherapy Advanced or Recurrent

Ovarian Cancer



# Advanced Ovarian Cancer Stage III, IV

- Surgical debulking has greatest survival impact
- Combination platinum-based chemotherapy
- Consolidation
  - GOG 178, AGO, MITO
  - 3 vs. 12
- Intraperitoneal chemotherapy
- Radiation
  - Thomas: Meta-analysis of 28 XRT studies are “unassessable”

# Initial Regimens

## Stage III

- Carboplatin/Taxol
  - AUC 5-7.5
  - 175 mg m<sup>2</sup>
- IP chemotherapy
  - Optimal < 1cm
  - Cisplatin/Taxol
  - Performance status, comorbidities
- Carboplatin/Taxotere
  - AUC 5-6
  - 60-75 mg/m<sup>2</sup>
  - Known neuropathy, DM
- Cisplatin/Taxol
  - Known or induced thrombocytopenia

# Salvage Chemotherapy

- Numerous agents FDA-approved
- Choice based on varying mechanism of action and toxicities
- NCCN guidelines:
  - Carbo/Taxol
  - Gemcitabine/Carbo
  - Single agent therapy

# Ovarian Cancer Surveillance

- Examination and CA-125
  - Every 2-4 months for 2 years
  - 6 months for 3 years
  - Annually after 5 years
- Imaging as clinically indicated
  - CT
  - PET/CT fusion

# Conclusions

1. Early stage disease is curable
  - o No chemo Stage IA, IB gr 1
2. Surgical success best outcome predictor
3. Initial chemotherapy
  - o Carbo/Taxol
  - o Carbo/Taxotere
  - o Carbo/Taxol IV/IP
4. Salvage chemotherapy
  - o Little advantage after *two* failed regimens



# NCCN Guidelines

## Ovarian Cancer

