Considerations for intraperitoneal vs intravenous chemotherapy

Fox Chase Cancer Center, USA
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Why Invade the Peritoneal Cavity?

• Is there a true "Pharmacokinetic Advantage"?
• Do we have unlimited access?
• Can we manage the complexity and complications?
• Have we identified Weapons of Mass Destruction?
• Can we afford the impact on drug development?
• Do we have international support for this mission?
• Have we analyzed all of the intelligence?

Initial Therapy of Ovarian Cancer
– Carboplatin (in combination with cyclophosphamide)
– Cisplatin (in combination with cyclophosphamide or paclitaxel)
– Paclitaxel (in combination with cisplatin)
– Doxorubicin, Melphalan, ThioTEPA

Recurrent Ovarian Cancer
– Carboplatin
– Paclitaxel, PEG-Liposomal Doxorubicin, Topotecan
– Gemcitabine (in combination with carboplatin)
– Altretamine, Hydroxyurea

No Indication in Ovarian Cancer
– Intraperitoneal delivery
– Maintenance or consolidation
– Ifosfamide, 5-Fluorouracil, Vinorelbine, Doxorubicin, Ora
– Etoposide, Irinotecan, Mesna, Melphalan, Tamoxifen
– Bevacizumab, Cetuximab, Imatinib, Gefitinib, Erlotinib, Telcyta, Ovarex, Xyotax
Case Fatality Ratio (Mean = 0.59)

9.02: Should dose intense therapy or intraperitoneal therapy be a standard arm of clinical trials in first line treatment?

There is no role for dose intense therapy with or without hematopoetic support or for intraperitoneal therapy as a standard arm in first line treatment.

Although there are randomised phase III clinical trials addressing the intraperitoneal route of cisplatin therapy in patients with minimal disease, interpretation of the results remains controversial, and therefore its use has not been widely adopted.

GOG172: Ovarian (optimal III)

- Epithelial Ovarian Cancer
- Optimal Stage III
- No prior therapy
- Elective Second-Look

Open: 23-Mar-98
Closed: 29-Jan-01
Accrual: 916 pts (evaluable)

GOG172: Assigned Treatment

<table>
<thead>
<tr>
<th>Maximum Cycles (N)</th>
<th>Intravenous (n=210)</th>
<th>Intraperitoneal (n=205)</th>
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<tbody>
<tr>
<td>Patients (N)</td>
<td>0-2</td>
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<td>3</td>
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</tbody>
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Armstrong, et al. NEJM 354:34--43, 2005
Session I

GOG172: Grade 3-4 Toxicity

![Graph showing ANC, Plt, Infections, GI, Neuro, Pain, and Metabolism categories with intravenous and intraperitoneal data.](image)


GOG172: Ovarian (optimal III)

![Graph showing progression-free survival and overall survival with CDDP/IP, Paclitaxel/IP (n = 208), and Paclitaxel/IV (n = 210).](image)


GOG172: Ovarian (optimal III) IP vs. IV

![Graph showing overall survival with CDDP/IP, Paclitaxel/IP (n = 208), Paclitaxel/IV (n = 210), and median survival of 43.7 months and 49.7 months, respectively.](image)


Meta-Analysis IP vs IV: Survival

![Graph showing survival rates with CDDP/IP, Paclitaxel/IP (n = 208), Paclitaxel/IV (n = 210), and median survival of 43.7 months and 49.7 months, respectively.](image)


Meta-Analysis IP vs IV: Toxicity

![Table showing toxicity comparison between CDDP/IP, Paclitaxel/IP (n = 208), and Paclitaxel/IV (n = 210).](image)

Meta-Analysis IP vs IV: Survival

![Table showing survival comparison between CDDP/IP, Paclitaxel/IP (n = 208), and Paclitaxel/IV (n = 210).](image)

Jaaaback K, Johnson N. Cochrane Database Systematic Reviews 2006

GOG0172: Points to Consider

- **The Recommended Regimen is Not Feasible**
  - Substitution of carboplatin for cisplatin not validated
  - Reduce cisplatin from 100 mg/m^2^ to 75 mg/m^2^ and/or schedule
  - Change paclitaxel infusion and/or schedule
  - Optimal number of cycles unclear

- **Role of Intraperitoneal Delivery Not Established**
  - Trial design flawed (too many variables)
  - Dose-intensity hypothesis (direct penetration) not validated
  - Impact of weekly paclitaxel not evaluated
  - Potential role of biology, angiogenesis, microenvironment

- **Net Clinical Benefit Unclear**
  - Only applicable to a minority of patients
  - Evolving standards (carboplatin and paclitaxel)
  - Competition with emerging biologic strategies

- **Impact on Future Research**
  - Dual (IP and IV) development pathways
  - Prioritization of clinical and financial resources
GOG158: Ovarian (optimal III)
- Epithelial Ovarian Cancer
- Optimal Stage III
- No prior therapy
- Elective Second-Look
- Non-Inferiority Design

Open: 03-Apr-85
Closed: 26-Jan-98
Accrual: 792 pts (evaluable)

GOG172: Ovarian (optimal III)
- Epithelial Ovarian Cancer
- Optimal Stage III
- No prior therapy
- Elective Second-Look

Open: 23-Mar-88
Closed: 29-Jan-01
Accrual: 416 pts (evaluable)

GOG172 & 158: Exploratory Analysis

GOG: Combined Exploratory Analysis

GOG0182-ICON5: Overall Survival

Ptomeaic View of Ovarian Cancer
Session I

GOG 0126 Phase II Overall Response

- Phase II Platinum-Resistant
- Response Rate (CR+PR) 10%-90% CI
- Protocol 0126 Section

GOG 0126 & 0170 Phase II Response

- Phase II Platinum-Resistant and Biologics

GOG218: CP +/- Bevacizumab

- Paclitaxel 175 mg/m² (3 h)
- Carboplatin AUC=6.0
- Bevacizumab 15 mg/kg q21d*

IIII

Placebo (14 m total)

II

Paclitaxel 175 mg/m² (3 h)
Carboplatin AUC=6.0
Bevacizumab 15 mg/kg q21d*

Placebo (14 m total)

Open: 26-Sep-05
Closed: -
Target Accrual: 2000 pts (3 Y)

Intratumoral Lymphocytes & Survival

  - Retrospective analysis from biospecimen repository (Turin Italy)
  - Overall analysis included 174 evaluable patients
  - Subset of 74 evaluable patients with clinical CR after primary therapy
  - Optimal residual defined as < 1 cm

Burger et al., J Clin Oncol 20:5180-8, 2002
Michael A. Bookman

TREG in Ovarian Cancer

All Patients (n=70)

Patients divided into three equal groups on the basis of TREG numbers:
- Low TREG group included cell count of 101 or less per mm^3 (n=24)
- High TREG group included a cell count of 345 or more per mm^3 (n=29)
- Medium TREG cell group included the remainder (n=27)


Enlightened View of Ovarian Cancer

Biology

Carboplatin AUC=6 (IV)
Paclitaxel 175 mg/m^2 (d1, 3h) (d1, 3h)
Bevacizumab (C2+)
Cisplatin 75 mg/m^2 (IP)
Paclitaxel 135 mg/m^2 (d1, 3h) (d1, 3h)
Paclitaxel 60 mg/m^2 (d8, IP) (d8, IP)
Bevacizumab (C2+)

If IP Therapy is Really So Important...

- Why has it been more than 3 years without an active IP trial for women with ovarian cancer and optimal cytoreductive surgery?
- Where is the funding to support scientific investigation of IP therapy using generic off-patent medications (cisplatin and paclitaxel)?
- Are we prepared to evaluate all new agents "IP" and "IV"?
- Should IP therapy have a higher priority than evaluation of targeted agents, immunomodulation, and tumor molecular profiling?

GOG-OVM0705: Ovarian (optimal III)

- Proposal under development
- Epithelial Ovarian Cancer
- Optimal Stage III
- No prior therapy

Phase III
- OS primary endpoint

Open: Closed: Accrual:

I
- Carboplatin AUC=6 (IV)
- Paclitaxel 175 mg/m^2 (d1, 3h)
- Bevacizumab (C2+)
- Bevacizumab (maint)

II
- Carboplatin AUC=6 (IP)
- Paclitaxel 175 mg/m^2 (d1, 3h)
- Bevacizumab (C2+)
- Bevacizumab (maint)

III
- Cisplatin 75 mg/m^2 (IP)
- Paclitaxel 135 mg/m^2 (d1, 3h)
- Paclitaxel 60 mg/m^2 (d8, IP)
- Bevacizumab (C2+)
- Bevacizumab (maint)

GOG-OVM0705: Ovarian (optimal III)

NCI Clinical Announcement (05-JAN-2006)

- Reduction in Peer-Reviewed Support
  - Fewer investigator-initiated trials
- Reduced NCI Support for National Cooperative Groups
  - Currently operating at level funding (after attempted 20% cut)
- Closure of active trials due to insufficient resources
- Closure of disease-specific working groups
- Increased Reliance on Industry Support
  - National Cooperative Groups managing "industry" trials
- Difficult to prioritize science ahead of fiscal support
- Restructuring Developmental Therapy
  - The number and diversity of molecular-targeted agents poses a fundamental challenge to our traditional clinical research infrastructure
  - Alternative routes of drug administration multiples the challenge

Analysis: Scientific and Fiscal Realities
Do we really need this debate?

Tony Auth, Philadelphia Inquirer, Mar 08

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Curriculum Vitae

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Personal:
Born 02-Apr-54 in Quincy, Massachusetts
Citizen of the United States
Married to Maria Pia Platia, MD
Children, Elisa Pia (04-Dec-86) and Laura Michela (12-Jun-89)

Education and Professional Degrees:
Sep 76 - Jun 80 Harvard Medical School MD (Jun 80) Boston, Massachusetts
Sep 72 - Sep 76 Massachusetts Institute of Technology Cambridge, Massachusetts
Brain and Cognitive Sciences SM (Sep 76) Interdisciplinary Science (Biology) SB (Jun 76)
Sep 68 - Jun 72 Braintree High School Braintree, Massachusetts
Academic Appointments:

Mar 07 - present  Vice President, Ambulatory Care and Clinical Research
Apr 02 - Mar 07  Medical Director, Ambulatory Care and Clinical Information Systems
Jan 96 - present  Director, Protocol Management Facility (NCI-Approved PRMS)
Oct 94 - present  Director, Medical Information Management Program
Jul 93 - present  Director, Medical Gynecologic Oncology
Apr 99 - present  Attending Physician and Member
Nov 88 - Mar 99  Attending Physician and Associate Member

Department of Medical Oncology Division of Medical Science Fox Chase Cancer Center, Philadelphia, PA
Jan 99 - May 02  Outcomes Database Consultant

National Comprehensive Cancer Network, Philadelphia, PA
Jul 86 - Nov 88  Senior Staff Fellow, Medical Oncology
Medicine Branch and Biological Response Modifiers Program National Cancer Institute, National Institutes of Health Bethesda, Maryland
Jul 83 - Jun 86  Medical Staff Fellow, Medical Oncology (Fellowship) Medicine Branch National Cancer Institute, National Institutes of Health Bethesda, Maryland
Jul 80 - Jun 83  Clinical Fellow in Medicine (Internship and Residency, Internal Medicine)
Beth Israel Hospital, Harvard Medical School Boston, Massachusetts

Certification:
Subspecialty Board, Medical Oncology 092489 (Nov 85)
American Board of Internal Medicine 092489 (Sep 83)
National Board of Medical Examiners 227115 (Jul 81)

Licensure and Course Certification:
Pennsylvania Board of Medicine MD-042886-E (Oct 88, active)
Maryland Board of Medical Examiners D33641 (May 86, inactive)
DEA BB0489422
NCI Investigator 15013
NIH OHSR Protection of Human Research Subjects 975675987 (Dec 00)
FCCC Protection of Human Research Subjects (Mar 02, Sep 03)

Membership:
Pennsylvania Medical Society (02401800134) (Sep 98)
International Gynecologic Cancer Society (IGCS) (Jan 93)
American Association of Immunologists (AAI) (May 87)
Clinical Immunology Society (CIS) (Jul 87)
American Society of Clinical Oncology (ASCO) (May 89)
American Association for Cancer Research (AACR) (Aug 89)

Honors:
First Robert L. Krigel Memorial Award for Excellence in Teaching and Clinical Oncology (Jun 94)

Teaching:
Temple University Medical School
Jan 98 - Apr 98  Introduction to Clinical Medicine
Nov 88 - Apr 02  Supervision of medical residents and students (inpatient)
Nov 88 - present  Supervision of medical oncology fellows (inpatient and outpatient)

Committees:
Gynecologic Oncology Group (GOG)
Jan 00 - present  Principal Investigator, FCCC
**Session I**

Feb 93 - Jan 00  Co-Principal Investigator, FCCC  
Nov 95 - Jul 06  Chairman, Developmental Therapeutics Committee  
Feb 97 - present  Chairman, Information Technology Committee  
Jul 06 - present  Member, Operations Committee  
Nov 95 - present  Member, Protocol Committee  
Feb 93 - present  Member, Phase-I Subcommittee  
Feb 93 - present  Member, Medical Oncology Committee  
Feb 97 - Dec 02  Member, Committee on Experimental Medicine  
Oct 99 - Jan 02  Member, Management Committee  
Jan 01 - Jul 06  Member, Chairman’s Management Committee  

**Fox Chase Cancer Center (FCCC)**  
Jan 02 - present  Chairman, Clinical Projects Executive Steering Team (Medical Informatics)  
Sep 94 - May 02  Chairman, Research Review Committee (Clinical Research Protocols)  
Sep 94 - present  Member, Research Review Committee  
May 02 - present  Member, Executive Committee of Staff  
Aug 99 - present  Member, Performance Monitoring Committee  
Dec 90 - present  Scientists Advisory Committee, Research Computing  
Apr 97 - present  Ambulatory Care Committee  
Apr 97 - present  Tumor Registry Committee  
Aug 89 - Jan 94  Medical Computer Committee  
Nov 88 - Dec 90  Pharmacy and Therapeutics Committee  

**National Comprehensive Cancer Network (NCCN)**  
May 95 - present  Outcomes Committee  
May 96 - present  Breast Cancer Outcomes Pilot Committee  
May 96 - present  Guidelines Committee, Cancer of the Cervix and Uterus  

**American Society of Clinical Oncology (ASCO)**  
Jun 95 - May 96  Program Committee, Gynecologic Oncology  
Jun 89 - May 90  Program Committee, Gynecologic Oncology  
Jun 95 - May 96  Ad Hoc Committee to Develop ASCO Online  

**International Gynecologic Cancer Society (IGCS)**  
Jun 94 - Sep 95  Scientific Program Committee  
Jul 06 - present  Director, Office of Educational Resources  

**National Institutes of Health (NIH)**  
Jul 07 - present  Member, Ovarian Task Force, Gynecologic Cancer Steering Committee  
Jun 86 - Nov 88  Chairman, Ambulatory Care Committee  
Jun 86 - Nov 88  Hospital Infection Committee  
Jul 84 - Jun 86  Medical Staff Fellowship Committee Beth Israel Hospital, Harvard Medical School  
Jul 82 - Jun 83  Laboratory Board  

**Editorial Boards:**  
Jun 99 - present  Board Member, Gynecologic Oncology (Academic Press)  
Jan 01 - Dec 03  Board Member, Journal of Clinical Oncology (WB Saunders)  
Jan 96 - Dec 98  Board Member, Journal of Clinical Oncology (WB Saunders)  
Jan 96 - present  Board Member, Oncology (S. Karger AG)  
Jan 95 - Dec 01  Board Chairman, Oncology Online (Oncology Therapeutics Network)  

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