The Value of PROs in a Phase II Intraperitoneal Chemotherapy Trial for Ovarian Cancer: A GOG Study

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Background: Epithelial ovarian cancer

- Ovarian cancer leading cause of death from gyn malignancies
- 22,220 diagnosed in 2005 and 16,210 died
- Disease spread by intra-abdominal dissemination to other sites in peritoneal cavity and lymphatic spread

Background: Treatment

- Primary surgery: Dx, staging, cytoreduction
- Initial chemotherapy: IV platinum-taxane combination q 3 wks for 6 courses
- Over 10 yrs, 7 trials assessing IP associated with a 21% decrease in risk of death
- Expected survival is 4 years, this size reduction in overall death rate translates to 12-month increase in overall median survival

Importance of IP Therapy

- The magnitude of improvement in median overall survival associated with IP/IV administration of chemotherapy is similar to that observed with the introduction of either cisplatin or paclitaxel
  - NCI Clinical Announcement 12/05

GOG #172

Armstrong et.al. Abs #803, ASCO 2002

BRCA Analysis
DNA Banking

Second look
Laparotomy
(if chosen)

Ovarian cancer
Optimal (<1cm)
Stage III
Stratify:
Gross residual
Planned 2nd look

RANDOMIZE

Paclitaxel 135 mg/m²/24h
Cisplatin 75 mg/m²
q 21 days x 6

Paclitaxel 135 mg/m²/24h
Cisplatin 100 mg/m² IP D2
Paclitaxel 60 mg/m² IP D8
q 21 days x 6

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Results on Survival

Armstrong et al. NEJM, 2006

	Intravenous	Intraperitoneal
Progression-free	18.3 mos	23.8 mos
Overall Survival	49.7 mos	65.6 mos

Completion of Assigned Therapy

Cycles	Intravenous (%)	Intraperitoneal (%)
0	100	92
1	96	74
2	92	59
3	86	52
4	86	47
5	84	42
6	83	42

Toxicities

- Toxicity associated with presence of an IP catheter (Walker et al, 2006)
  - Infection, catheter blockage/leak, access
- Toxicity associated with the IP administration of chemotherapy
  - Abdominal pain, bowel complications
- Toxicity associated with the chemotherapy

Results on Toxicities

CTC Grade >=3	Intravenous (N=210)	Intraperitoneal (N=201)
Fatigue	4 %	18 %
Neurologic event	9 %	19 %
Pain	1 %	11 %

Results of GOG 172

- The IP regimen used higher and more frequent dosing than the IV regimen
- Toxicities were greater on the IP arm
- Fewer patients on the IP arm were able to complete 6 cycles of therapy
- A statistically significant improvement in PFS and OS for patients in the IP arm
- The 65.6 month median survival on IP is the longest survival reported to date from an advanced OC randomized trial

Quality of Life Assessment

- FACT-O (FACT-G: 27 items; Ovarian subscale: 12 items)
- FACT-GOG/NTX: 11 items
- FACT-GOG/Abd Discomfort: 4 items

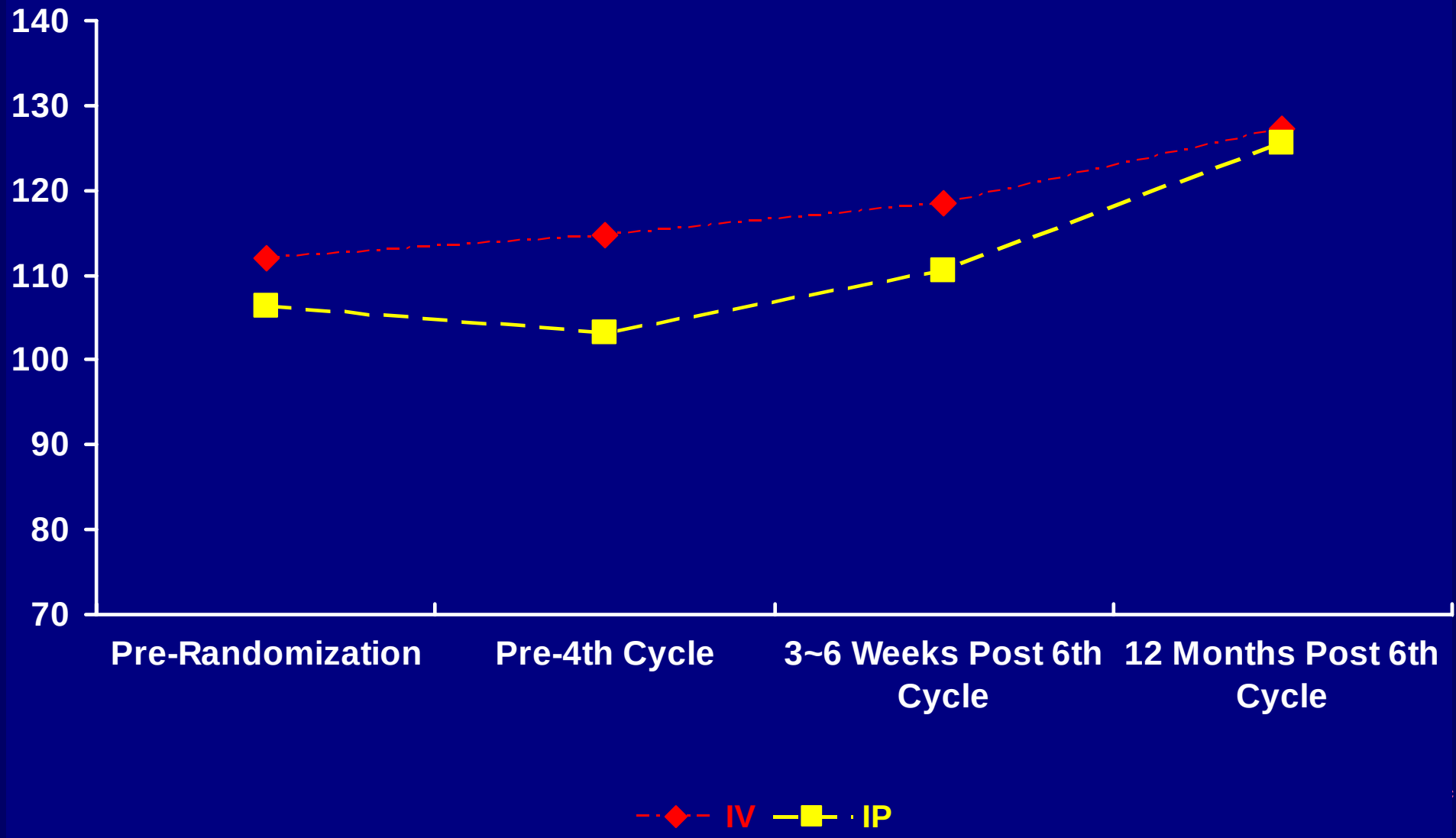
Assessment Intervals

- Prior to Randomization
- Prior to chemotherapy cycle 4
- 3-6 weeks after chemotherapy cycle 6
- 12 months after the completion of cycle 6

Results – FACT-O

- QOL was significantly worse in the IP group before cycle 4 and 3-6 weeks after treatment ($P<0.01$)
- No significant QOL differences at one year

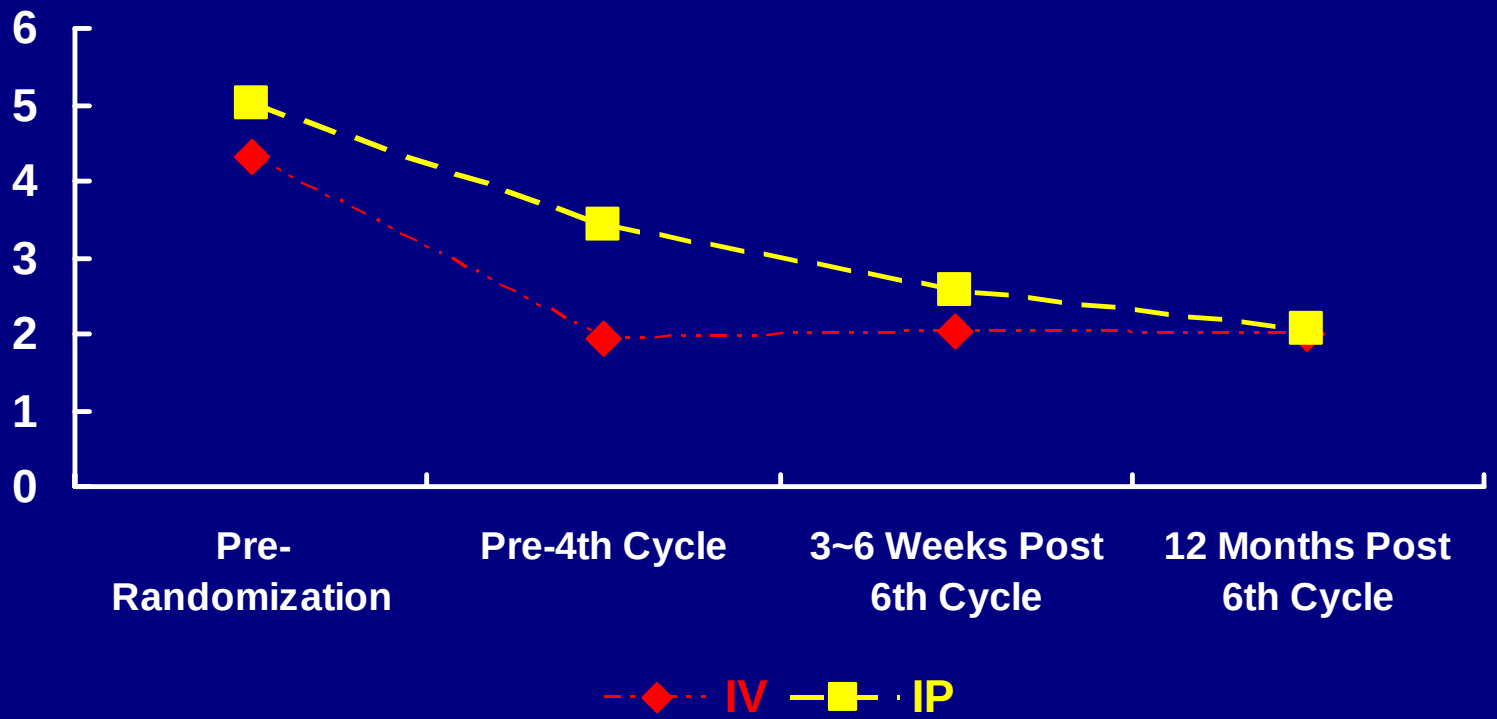
Patient-Reported FACT-O Scores



Results – Abdominal Discomfort

- Abdominal Discomfort was significantly worse in the IP arm prior to cycle 4 ($P<0.0001$)

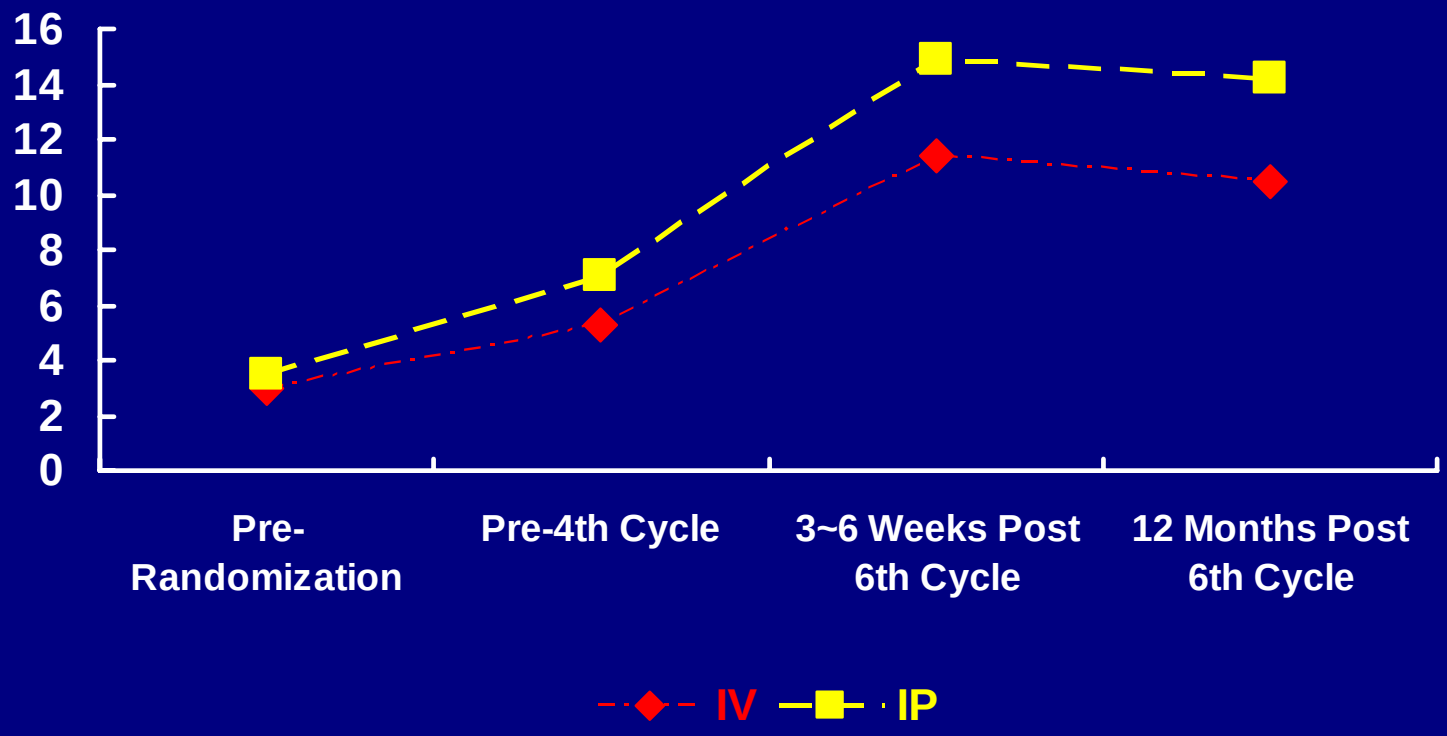
Patient-Reported Abdominal Discomfort Scores



Results - Neurotoxicity

- Neurotoxicity was significantly worse in the IP arm 3-6 weeks after completing chemotherapy (P=0.0004)
- Neurotoxicity was significantly worse in the IP arm one year later (P=0.0018)

Patient-Reported Neurotoxicity Scores



Phase III Trial Conclusions

- Pts who received higher dose IP therapy, compared to those with conventional dose IV therapy experienced
  - More QOL disruption
  - More abdominal discomfort
  - More neurotoxicity
  - HOWEVER, better recurrence-free and OS

Phase III Trial Conclusions

- From Baseline to 12 months after treatment
  - Overall QOL improved in both groups
  - Attributed to physical, functional and ovarian-specific subscale improvements
  - Abdominal discomfort improved in both groups from pre-randomization to pre-4th cycle
  - Neurotoxicity worse over time in both groups, especially IP

Why is this NOT the standard of care?

- Toxicity
  - Increased myelotoxicity due to 24 hr taxol
  - Metabolic, renal, neurologic complications related to 100 mg/m cisplatin
  - Uncertain role of day 8 IP taxol on complications
- Logistical issues
  - High incidence of catheter-related failures
- Resource intensive
  - 2-day inpatient for 24 hr taxol infusion prior to IP cisplatin

PRO Data Implications?

- PRO data useful in interpreting treatment implications and influencing decision-making
- Illustrates complex relationship between treatment efficacy and toxicity

Implications for Future Studies

- Continued QOL evaluation critical to
  - Weigh considerable treatment benefits and toxicites
  - Assist in establishing guidelines and safety standards to buffer untoward effects

GOG 0226: Randomized Phase II Trial of IP Chemotherapy Regimens

- Regimen I: Paclitaxel 135 mg/m IV over 3 hrs Day 1 + Cisplatin 75mg/m IP Day 2 + Paclitaxel 60 mg/m IP on Day 8
- Regimen II: Paclitaxel 135 mg/m IV over 3 hrs Day 1 + Cisplatin 75mg/m IP Day 2
- Regimen III: Paclitaxel 135 mg.m IV over 3 hrs with IP cisplatin 75mg/m Day 1 +Paclitaxel 60 mg.m IP Day 8

Objectives

- To evaluate tolerability of regimens as proportion completing 6 cycles of assigned treatment
- To compare the 3 regimens:
  - Neuropathy (FACT-GOG/NTX4) (Huang et al, 2006)
  - Abdominal Discomfort (FACT-GOG/AD)
  - QOL (FACT-O-TOI)

Objectives-2

- Compare 3 regimens on proportion of pts requiring dose reductions or dose delays due to:
  - Neuropathy, abdominal pain, metabolic, renal, nausea/vomiting, IP catheter failure
- Assess PFS and OS

QOL Assessment

- FACT-O-TOI, GOG/NTX4, AD
- PROs completed:
  - Prior to randomization
  - Prior to cycles 2-6
  - Every 3 mos for one year after treatment completion

How Do PROs Contribute to this Phase II Study?

- "…more precise estimation of toxicity will be obtained by incorporating the FACT-O-TOI, NTX and AD subscales"
- "…will support development of a more acceptable treatment alternative, recognizing superiority of IP chemotherapy"

Conclusions

- Patient-reported outcomes of Phase III study supported development and evaluation of randomized Phase II study
  - Patient-reported outcomes represent key study objective in Phase II study
  - Consideration of accrual termination based on interim analyses of neurotoxicity PRO

Future Directions

- ***IP therapy will continue to play a role in the management of optimally debulked ovarian cancer***

- ***PROs will continue to have a prominent role in evaluating IP risks and benefits***