OVARIAN CANCER

INTRAPERITONEAL (IP) THERAPY

PACLITAXEL (INTRAVENOUS) – CISPLATIN (IP) –PACLITAXEL (IP)

Paclitaxel‡	135 mg/m^2	IV*	Day 1
	Followed by		
Cisplatin (INTRAPERITONEAL)	100 mg/m^2	IP**	Day 2
Paclitaxel (INTRAPERITONEAL)	60 mg/m^2	IP**	Day 8

‡Administer routine premedication; *Administer as a continuous infusion over 24 hours; **Reconstitute in 2000 mL of warmed normal saline and infuse as rapidly as possible through an implantable intraperitoneal catheter. See guidelines below for administration tips.

NOTE: Hold treatment for a serum creatinine of greater than 2 mg/dL.

Repeat every 21 days for 6 cycles.

Reference: Armstrong DK, et al. *N Engl J Med* 2006;354:34 – 43.

ACCESS: IP port vs peritoneal dialysis catheter:

Port – Accessed using right-angled (Huber) needle similar to IV or IA port. Can then infuse chemotherapy via normal parenteral tubing and bags. Fluid and chemotherapy left in to be resorbed. Gynecology Oncology Group (GOG) currently recommends a Bard 9.6, single lumen, venous access port

Catheter – Accessed via standard methods as in continuous ambulatory dialysis (CAD). Fluids must be infused via a bag with tubing or connector that can be connected to this apparatus. After the prescribed dwell time the chemotherapy may be drained out and disposed of via normal procedures for large volume chemotherapy

TOXICITY

Procedure Related:

Abdominal pain, nausea, vomiting, diarrhea, GI reflux, (all associated with abdominal distention and bowel spasm associated with increased fluid/pressure in the peritoneal cavity)
Shortness of breath due to increased intra-abdominal pressure
Vaginal leakage of IP fluid

Chemotherapy Related

Myelosuppression – agent dependent
Nephrotoxicity – Increased over that seen with IV nephrotoxic chemotherapy (cisplatin)
Neuropathy – peripheral (multiple agents) and auditory (platinum)
Nausea and vomiting are equal or greater with IP vs. IV chemotherapy agents
Antiemetics – serotonin $5HT_3$ antagonist plus corticosteroid, consider adding aprepitant if cisplatin used

ISSUES

For patient comfort

All fluids and chemotherapy should be warmed to body temperature for patient comfort, some regimens consider this optional
Loose expandable clothing should be worn (can be done as an outpatient)
Have patient void prior to procedure initiation; fracture bedpan can be used during the procedure PRN

For Patient Safety

Aggressive hydration required with and in-between therapies, IV if the patient can't keep up with PO.
Dialysis catheters may be more prone to infections, blockage, or leakage then a port
Port is more susceptible to needle dislodgment

To Facilitate Procedure

Patient placed on bedrest in semi-fowler's position throughout IP infusion
Head of bed inclined, bed no higher than 30 degrees, to decrease risk of needle dislocation during infusion and decrease pressure on the patient's diaphragm
Infuse 3-500 mL of warmed saline by gravity as rapidly as possible and observe patient for leakage or toxicity. If no untoward effects then start chemotherapy
Chemotherapy infused via gravity as rapidly as possible
After chemotherapy infuse 3-500 mL of additional warmed saline, then flush catheter per institutional guidelines and remove right angle needle
Reposition patient side to side every 15 minutes for 1 hour to disperse fluid throughout the abdominal cavity (may be optional)

Contraindications to IP chemotherapy

Disease outside the peritoneal cavity
Disease greater than 1 cm in the peritoneal cavity (ovarian)
Dense adhesions or fluid loculations in the peritoneal cavity

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Summary of IP chemotherapy provided by Joseph Bubalo, Pharm.D., BCPS, BCOP

OVARIAN CANCER

SYSTEMIC CHEMOTHERAPY

CAP (CYCLOPHOSPHAMIDE – DOXORUBICIN – CISPLATIN)

Cyclophosphamide	500 mg/m^2	IV	Day 1
Doxorubicin	50 mg/m^2	IV	Day 1
Cisplatin	50 mg/m^2	IV*	Day 1

*Administer routine pre- and post-hydration.

Repeat cycle every 21 days for 6 cycles.

Reference: ICON 3. *Lancet* 2002;360:505 – 15.

CARBOPLATIN

Carboplatin	AUC 5 or 6*	IV	Day 1

*AUC of 5 (Calvert formula) used if GFR determined by radioisotope or 24-hour urine collection
*AUC 6 (Calvert formula) used if GFR determined by Cockroft –Gault formula.

Repeat cycle every 21 days for 6 cycles.

Reference: ICON 3. *Lancet* 2002;360:505 – 15.

CARBOPLATIN – CYCLOPHOSPHAMIDE

Carboplatin	300 mg/m^2	IV*	Day 1
Cyclophosphamide	600 mg/m^2	IV	Day 1

*Administer over 1 hour.

DOSE MODIFICATION: If SCr rose (greater than 1.5 mg/dL in patients 45 kg and heavier or greater than 1.3 mg/dL in patients less than 45 kg) despite IV hydration, carboplatin was withheld and the cyclophosphamide dose was increased to 1000 mg/m^2.

Repeat cycles every 28 days for 6 cycles.

References: Swenerton K, et al. *J Clin Oncol* 1992;10:718 – 26; Alberts DS, et al. *J Clin Oncol* 1992;10:706 – 17.

CARBOPLATIN – PACLITAXEL

Carboplatin	AUC 5 or 6*	IV**	Day 1
	Followed by		
Paclitaxel‡	175 mg/m^2	IV***	Day 1

‡Routine premedication administered; *AUC of 5 (Calvert formula) used if GFR determined by radioisotope or 24-hour urine collection. AUC 6 (Calvert formula) used if GFR determined by Cockroft -Gault formula; **Administer over 30 minutes; ***Administer over 3 hours.

NOTE: The GOG published a randomized phase II trial comparing 3 versus 6 cycles of adjuvant carboplatin- paclitaxel. There was no difference in recurrence rate in recipients of 3 cycles, HOWEVER the dose of carboplatin in this trial was targeted to an AUC 7.5 compared to an AUC of 5 or 6 in most other randomized trials [Reference: Bell J, et al. *Gynecologic Oncol* 2006;102:432 – 9].

Repeat cycle every 21 days for 6 cycles.

References: ICON 3. *Lancet* 2002;360:505 – 15; Bolis G, et al. *J Clin Oncol* 2004;22:686 – 90; ICON 4. *Lancet* 2003;361:2099 – 106.

CISPLATIN

Cisplatin	100 mg/m^2*	IV	Day 1

*Routine pre- and post-hydration required.

Repeat cycle every 21 days to a maximum of 6 cycles.

Reference: Muggia FM, et al. *J Clin Oncol* 2000;18:106 – 15.

CISPLATIN – CYCLOPHOSPHAMIDE

Cyclophosphamide	600 mg/m^2	IV	Day 1
Cisplatin	75 mg/m^2	IV*	Day 1

*Administer over 3 hours with adequate pre- and post-hydration.

DOSE MODIFICATION: If SCr rose (greater than 1.5 mg/dL in patients 45 kg and heavier or greater than 1.3 mg/dL in patients less than 45 kg) despite IV hydration, cisplatin was withheld and the cyclophosphamide dose was increased to 1000 mg/m^2.

Repeat cycle every 28 days for 6 cycles.

References: Swenerton K, et al. *J Clin Oncol* 1992;10:718 – 26; Alberts DS, et al. *J Clin Oncol* 1992;10:706 – 17.

CISPLATIN – PACLITAXEL (INPATIENT)

Paclitaxel‡	135 mg/m^2	CIVI*	Day 1
Cisplatin	75 mg/m^2	IV**	Day 2

‡Routine premedication administered; *Administer as a continuous 24-hour infusion; **Administer at a rate of 1 mg/minute with adequate pre- and post-hydration.

Repeat cycle every 21 days for a total of 6 cycles.

References: McGuire WP, et al. *N Engl J Med* 1996;334:1 – 6; Markman M, et al. *J Clin Oncol* 2001;19:1001 – 7.

CISPLATIN – PACLITAXEL (OUTPATIENT)

Paclitaxel‡	175 mg/m^2	IV*	Day 1
	Followed by		
Cisplatin	50 – 75 mg/m^2	IV**	Day 1

‡Routine premedication administered; *Administer over 3 hours; **Administer pre- and post-hydration.

Repeat cycle every 21 days for 6 – 9 cycles.

References: Piccart MJ, et al. *J Natl Cancer Inst* 2000;92:699 – 708; ICON 4. *Lancet* 2003;361:2099 – 106.

DOCETAXEL

Docetaxel‡	35 mg/m^2	IV	Days 1, 8, 15, 22 and 29

‡Routine premedication administered.

Repeat cycle every 42 days.

Reference: Tinker AV, et al. *Gynecol Oncol* 2007;104:647 – 53.

DOCETAXEL – CARBOPLATIN

Docetaxel‡	75 mg/m^2	IV*	Day 1
	Followed immediately by		
Carboplatin	AUC 5**	IV***	Day 1

‡Routine premedication administered; *Administer over 1 hour; **AUC calculated using the Calvert formula; ***Administer over 1 hour.

Repeat cycle every 21 days for 6 cycles. Patients with PR or CR with an increased CA-125 could continue on single agent carboplatin to a targeted AUC of 7 for 3 additional cycles.

Reference: Vasey PA, et al. *J Natl Cancer Inst* 2004;96:1682 – 91.

DOCETAXEL – CARBOPLATIN

Docetaxel‡	35 mg/m^2	IV*	Days 1, 8, and 15
	Followed by		
Carboplatin	AUC 2**	IV***	Days 1, 8, and 15

‡Routine premedication administered; *Administer over 1 hour; **AUC calculated using the Calvert formula; ***Administer over 30 minutes.

NOTE: Maximum body surface area used was 2 m^2.

DOSE MODIFICATION: occurred if the following occurred: afebrile grade 4 neutropenia lasting more than 7 days, grade 4 neutropenia with fever, grade 3 anemia, grade 3 renal toxicity, hepatic toxicity (bilirubin > ULN or transaminases > 5 x ULN), uncontrolled grade 3 nausea/vomiting, grade 2 stomatitis, other grade 2 non-hematologic toxicities with an impact on organ function, and omission of 2 consecutive weekly doses. Grade 3 peripheral neuropathy required omitting doses for a maximum of 2 weeks, until recovered to grade 2, and a reduction of one dose level. The first dose modification decreased the Docetaxel to 30 mg/m^2 and the second dose modification decreased the carboplatin dose to an AUC of 1.

Repeat cycle every 28 days until evidence of disease progression, unacceptable toxicity, or 2 cycles beyond complete remission.

Reference: Kushner DM, et al. *Gynecol Oncol* 2007;105:358 – 64.

DOCETAXEL – CISPLATIN

Docetaxel‡	75 mg/m^2	IV*	Day 1
	Followed by		
Cisplatin	75 mg/m^2	IV**	Day 1

‡Routine premedications administered; *Administer over 1 hour; **Administer over 4 hours with adequate pre- and post-hydration.

Repeat cycle every 21 days for 6 cycles.

Reference: Vasey PA, et al. *J Clin Oncol* 1999;17:2069 – 80.

GEMCITABINE

Gemcitabine	1000 mg/m^2	IV*	Days 1 and 8

*Administer over 30-60 minutes.

NOTE: Cytokines were permitted for patients in patients demonstrating neutropenia for more than 7 days or febrile neutropenia.

Repeat cycle every 21 days until disease progression or unacceptable toxicity.

Reference: Mutch DG, et al. *J Clin Oncol* 2007;25:2811 – 8.

GEMCITABINE - CARBOPLATIN

Gemcitabine	1000 mg/m^2	IV	Days 1 and 8
Carboplatin	AUC 4	IV	Day 1

NOTE: AUC was based on the Calvert formula. The AUC calculation was based on GFR calculation according to the formula of Jelliffe.

Repeat cycle every 21 days to a maximum of 10 cycles.

Reference: Pfisterer J, et al. *J Clin Oncol* 2006;24:4699 - 707.

GEMCITABINE - CISPLATIN

Gemcitabine	1000 mg/m^2	IV*	Days 1 and 15
	Followed by		
Cisplatin	40 mg/m^2	IV*	Days 1 and 15

*Administer over 30 minutes; **Administer over 60 minutes with adequate pre- and post-hydration.

DOSE MODIFICATION: in the event of febrile neutropenia or grade 3 or 4 neutropenia despite colony-stimulating factors on day 1 or day 15, the doses of cisplatin and gemcitabine were reduced by 20%. If thrombocytopenia persisted for 2 weeks the same dose reductions occurred. Cisplatin was withheld for ototoxicity (grade 2), neurotoxicity (grade 3), or renal toxicity (grade 2), and was continued at 80% of the dose if patients improved.

Repeat cycle every 28 days for a maximum of 6 cycles.

Reference: Bozas G, et al. *Gynecol Oncol* 2007;104:580 - 5.

GEMCITABINE - LIPOSOMAL DOXORUBICIN

Liposomal Doxorubicin	30 mg/m^2	IV*	Day 1
	Followed by		
Gemcitabine	1000 mg/m^2	IV**	Days 1 and 8

*Administer over 60 minutes; **Administer over 30 minutes.

NOTE: Patients who had delayed treatment for more than 2 weeks and in the case of hypersensitivity reactions, treatment was discontinued. In the presence of grade 4 hematological toxicity, the doses of gemcitabine and liposomal doxorubicin were reduced by 20% the following cycle. If hand-foot syndrome developed, the dose of liposomal doxorubicin was reduced by 20% in the next cycles. G-CSF and/or erythropoietin were administered for hematological toxicity according to ASCO guidelines.

Repeat cycle every 21 days.

Reference: Ferrandina G, et al. *Gyn Oncol* 2005;98:267 - 73.

LIPOSOMAL DOXORUBICIN

Liposomal doxorubicin	50 mg/m^2	IV*	Day 1

*Administer over 1 hour.

Repeat cycle every 28 days for up to 1 year.

NOTE: Mutch, et al. recommended stopping liposomal doxorubicin when the cumulative lifetime dose reached 500 mg/m^2.

References: Mutch DG, et al. *J Clin Oncol* 2007;25:2811 – 8; Gordon AN, et al. *J Clin Oncol* 2001;19:3312 – 22; Gordon AN, et al. *Gynecol Oncol* 2004;95:1 – 8.

PACLITAXEL

Paclitaxel‡	135 mg/m^2	CIVI*	Day 1

‡Routine premedication administered; *Administer as a continuous infusion over 24 hours.

Repeat cycle every 21 days.

Reference: Trimble EL, et al. *J Clin Oncol* 1993;11:2405 – 10.

PACLITAXEL (MAINTENANCE)

Paclitaxel‡	135 mg/m^2	IV*	Day 1

‡Routine premedication administered; *Administer over 3 hours.

NOTE: Protocol modified and dose reduced to 135 mg/m^2 after excessive toxicity identified.

Repeat cycle every 28 days for 12 cycles.

Reference: Markman M, et al. *J Clin Oncol* 2003;21:2460 – 5.

PACLITAXEL – GEMCITABINE

Paclitaxel ‡	80 mg/m^2	IV*	Days 1, 8 and 15
	Followed by		
Gemcitabine	1000 mg/m^2	IV**	Days 1, 8 and 15

‡Routine premedication administered; *Administer over 1 hour; **Administer over 30 minutes.

Repeat cycle every 28 days.

Reference: Garcia AA, et al. *Gynecol Oncol* 2004;93:493 – 8.

PEGYLATED DOXORUBICIN – CARBOPLATIN

Liposomal doxorubicin	30 mg/m^2	IV*	Day 1
	Followed by		
Carboplatin	AUC 5**	IV***	Day 1

*Administer over 1 hour; **AUC calculated by Calvert formula, maximum dose was 800 mg; ***Administer over 30 minutes.

DOSE MODIFICATION: If the ANC was < 0.5 x 10^9/L for ≥ 7 days or ANC < 0.1 x 10^9/L for 3 days, febrile neutropenia or an infection requiring intravenous antibiotics and/or hospitalization, a platelet count < 25 x 10^9/L, or bleeding requiring platelet transfusion – the dose of pegylated doxorubicin was reduced to 25 mg/m^2 and carboplatin to an AUC of 4. Treatment was delayed for an ANC < 1.5 x 10^9/L and platelets < 100 x 10^9/L with dose reductions of both drugs as above assuming adequate recovery by day 42.

Repeat cycle every 28 days for a maximum of 9 cycles.

Reference: Ferrero JM, et al. *Ann Oncol* 2007;18:263 – 8.

TAMOXIFEN

Tamoxifen	20 mg BID	PO	Ongoing

Reference: Markman M, et al. *Gynecol Oncol* 1996;62:4 – 6.

TOPOTECAN

Topotecan	1.5 mg/m^2/day	IV*	Days 1 – 5

*Administer over 30 minutes.

Repeat cycle every 21 days.

References: Bookman MA, et al. *J Clin Oncol* 1998;16:3345 – 52; McGuire WP, et al. *J Clin Oncol* 2000;18:1062 – 7.

TOPOTECAN

Topotecan	1.5 mg/m^2/day	IV*	Days 1 – 3

*Administer over 30 minutes.

Repeat cycle every 21 days to a maximum of 6 cycles.

Reference: Markman M, et al. *Gynecol Oncol* 2000;79:116 – 9.

TOPOTECAN (WEEKLY)

Topotecan	4 mg/m^2	IV*	Weekly

*Administer over 30 minutes.

Repeat dosing until toxicity, intolerance, or progressive disease or patients completed a maximum of 6 months of therapy following documentation of a complete or partial response.

DOSE MODIFICATION: The dose was reduced in 0.5 mg/m^2 increments for any grade 3 or 4 hematologic or nonhematologic toxicity. The dose was reduced by 1 mg/m^2 for patients with febrile neutropenia complications. Chemotherapy was delayed in patients with an ANC $\leq$ 1.5 x 10^9/L or a platelet count of $\leq$ 100 x 10^9/L.

Reference: Spannuth WA, et al. *Gynecol Oncol* 2007;104:591 – 5.

VINORELBINE

Vinorelbine	30 mg/m^2	IVB*	Days 1 and 8

*Administer as an IV bolus.

Repeat cycle every 21 days to a maximum of 8 cycles.

Reference: Sorensen P, et al. *Gynecol Oncol* 2001;81:58 – 62.