Intraperitoneal Chemotherapy for Stage IV Gastric Cancer

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Outline

- Rationale for catheter-based intraperitoneal chemotherapy
- Comparison to other intraperitoneal treatment approaches
- Clinical trial at the National Cancer Institute
- Future directions

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Clinical Need

- Cytoreduction and HIPEC are reserved for low-volume disease
- However, many patients will present with more extensive disease
    - Some may become candidates for CRS/HIPEC after effective treatment

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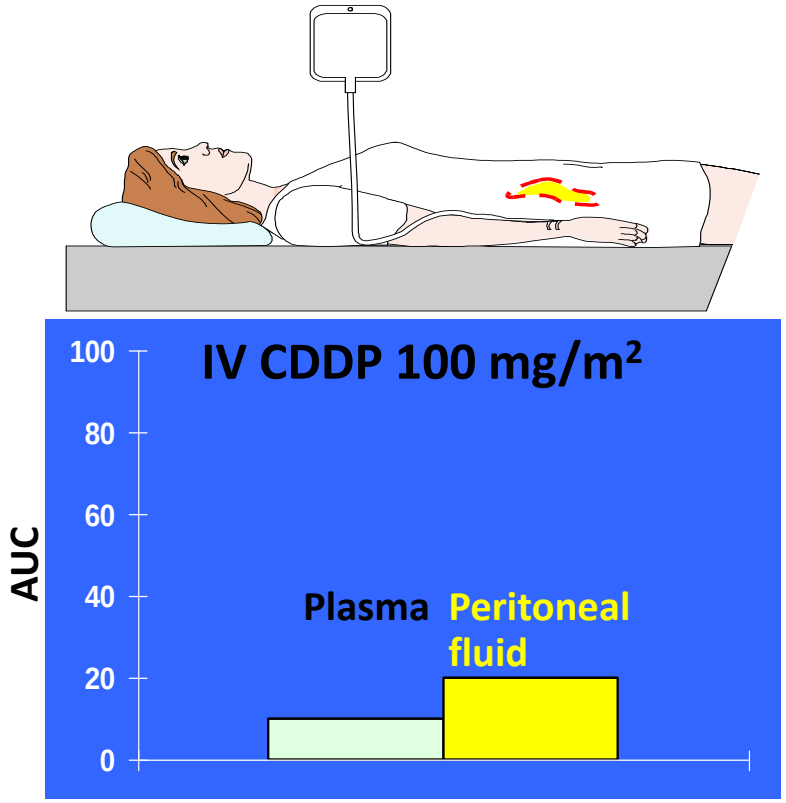
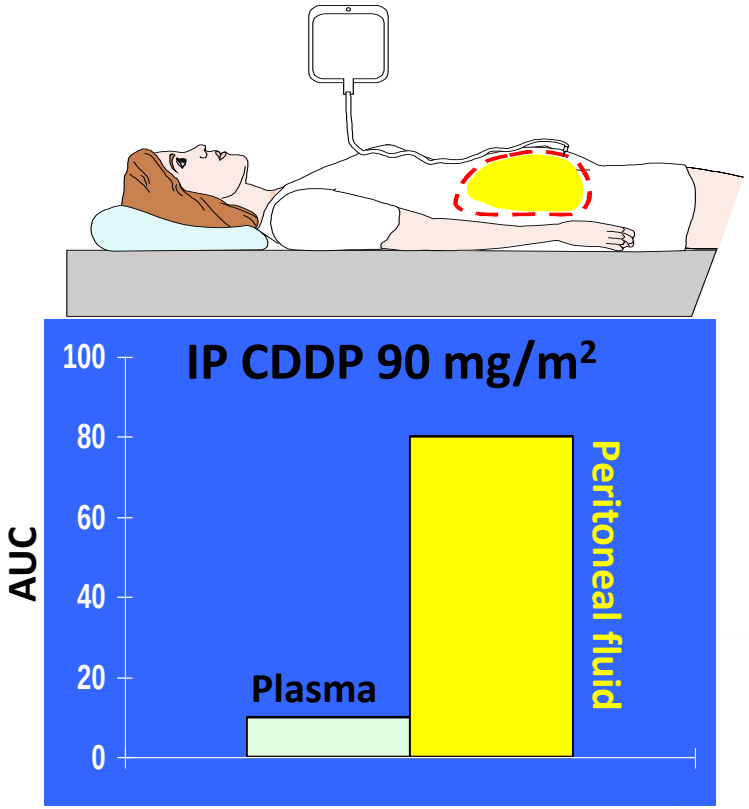
Why an Intraperitoneal Approach?





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Rationale for Catheter-Based Chemotherapy

- Allows for use of chemotherapy drugs that:
  - Do not require heat to improve efficacy
  - Are cell-cycle specific

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Chemotherapeutic Agents

Drug	Molecular weight	Type	AUC ratio	$T^{1/2}$ (mins)	$T^{80\%}$ (mins)	Dose	Carrier solution	Incompat-ability in solution	Heat synergy	Heat stability	Depth of penetratio
Doxorubicin	579.99	Antitumor antibiotic	230	20	80	15 mg/m^2	1.5% dextrose dialysis solution	Heparin, fluorouracil	Yes	42 °C	4-6 cell layers
DOXIL (liposomal doxorubicin)	579.99	Antitumor antibiotic	1,040	180	NA	100 mg/m^2	1.5% dextrose dialysis solution	Heparin, fluorouracil	Yes	42 °C	4-6 cell layers
Etoposide	588.58	Antitumor antibiotic	65	NA	NA	25-350 mg/m^2	5% dextrose	Plastic devices; acrylics; antibiotics	Yes	42 °C	NA
5-fluorouracil	130.08	Anti-metabolite	280	30	75	650 mg/m^2 (×5 days)	0.9% sodium chloride; 1.5% dextrose dialysis solution; Icodextrin	Doxorubicin daunorubicin idaurubicin cisplatin diazepam icytarabine	Minimal	43 °C	0.2 mm
Floxuridine (FUDR)	246.2	Anti-metabolite	75	NA	NA	500 mg/m^2 twice daily (×3 days)	0.9% sodium chloride	NA	Minimal	43 °C	NA
Gemcitabine	299.5	Pyrimidine antagonist	205	40	75	1,000 mg/m^2	0.9% sodium chloride	NA	At 48 hours	42.5 °C	NA
Irinotecan	677.19	Antitumor antibiotic	NA	NA	NA	200 mg/m^2	1.5% dextrose dialysis solution	NA	No	44 °C	NA
Melphalan	305.2	Alkylator	56	33	69	70 mg/m^2	0.9% sodium chloride	NA	Marked	42 °C	NA
Mitomycin C	334.3	Antitumor antibiotic	27	40	90	15 mg/m^2	1.5% dextrose dialysis solution	Bleomycin	Yes	42.5 °C	2,000 μm
Mitoxantrone	517.41	Antitumor antibiotic	115-255	NA	NA	28 mg/m^2	0.9% sodium chloride; lactated Ringer's solution	Heparin	Yes	43 °C	5-6 cell layers
Pemetrexed	471.4	Multi-targeted antifolate	70	90	260	500 mg/m^2	1.5% dextrose dialysis solution	NA	NA	NA	NA
Carboplatin	371.25	Alkylator	10	NA	NA	300 mg/m^2	0.9% sodium chloride	NA	Yes	41.5 °C	0.5 mm
Cisplatin	300.1	Alkylator	10	30	90	90 mg/m^2	0.9% sodium chloride	NA	Yes	41.5 °C	1-3 mm
Oxaliplatin	397.3	Alkylator	16	40	60	460 mg/m^2	5% dextrose	Aluminum alkaline or NaCl solutions	Yes	46 °C	1-2 mm
Paclitaxel	853.9	Antimitotic	1,000	NA	NA	120-180 mg (total dose)	1.5% dextrose dialysis solution; 6% hetastarch	Plastic containers and tubes	No	42.5 °C	>80 cell layers

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Why Paclitaxel?

- High molecular weight, hydrophobic
- Targets cells that are actively dividing
- Effects are seen as early as 6 hours, last as long as 72 hours
- Ideal agent for bidirectional therapy

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Rationale for Bidirectional Therapy

- Treat peritoneal nodules using intraperitoneal and intravenous drugs
- IV chemotherapy is thought to diffuse into the peritoneal space
  - Leakage facilitated by the increased vascularity of tumor nodules
- Co-administration of IP chemo injures or collapses blood vessels
  - This leads to increased cell death in the outer layers of the nodules

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Intraperitoneal Chemotherapy: Advantages

Catheter-Based

- Does not require the OR
- Can be given with IV chemo

Laparoscopy-Based

- Ability to control perfusion
- Can augment with heat

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Cancer Treat Rep 1978.

Intraperitoneal Chemotherapy: Disadvantages

Catheter-Based

- Inability to control perfusion
- Cannot augment with heat
- Catheter-related complications

Laparoscopy-Based

- Does require the OR
- Timing offset with IV chemo

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Cancer Treat Rep 1978.

Prior Experience in Gastric Cancer

Author	Trial Design	Intervention	Recommended Dose	Accrual	Toxicity	Treatment Response	Survival
Ishigami, H. et al (2009)	Phase 1	PAX (IP/IV) S-1 (PO)	PAX IV 50mg/m^2 PAX IP 20mg/m^2 S-1 PO 80mg/m^2/day	n = 9 patients	Dose level 1 - n= 4 grade 3/4 (leukopenia/neutropenia) Dose level 2 - n = 4 grade 3 (leukopenia/neutropenia/diarrhea)	6/7 patients converted to negative cytology	N/A
Kurita, N. et al (2011)	Phase 1	PAX (IP) S-1 (PO) Gastrectomy	PAX IP 40mg/m^2 S-1 PO 80mg-100mg/day	n = 18 patients	Dose level 2 - n=1 grade 3 (leukopenia) Dose level 5 - n=2 grade 3 (leukopenia)	2/18 patients converted to negative cytology, 2/18 PR, 15/18 SD	Median OS 11mo
Ishigami, H. et al (2009)	Phase II	PAX (IV/IP) S-1 (PO)	PAX IV 50mg/m^2 PAX IP 20mg/m^2 S-1 PO 80mg/m^2	n = 40 patients	Grade 3/4 - leukopenia (18%), neutropenia (38%), anemia (10%), Anorexia (5%), N/V (8%), diarrhea (3%)	24/40 patients converted to negative cytology, 10/40 PR, 6/40 SD	1-yr OS 78%, Median OS 22.5mo
Imano, M et al (2012)	Phase II	PAX (IP) One Dose PAX (IV) S-1 (PO)	PAX IV 80mg/m^2 PAX IP 80mg/m^2 S-1 PO 80mg/m^2/day	n = 35 patients	Grade 3/4 - anemia (5.7%), leukopenia (8.6%), neutropenia (22.8%), ALT elevation (5.7%)	15/22 reduction in gastric wall thickening 1/8 Target Lesion CR 1/7 Target Lesion PR	1yr OS 68.6%, Median OS 21.3mo
Yamaguchi, H et al (2013)	Phase II	PAX (IP/IV) S-1 (PO)	PAX IV 50mg/m^2 PAX IP 20mg/m^2 S-1 PO 80mg/m^2	n = 35 patients	Grade 3/4 - neutropenia (34%), leukopenia (23%), anemia (9%)	5/7 Target Lesion OR 28/35 converted to negative cytology	1yr OS 77.1%, 2yr OS 44.8%, Media OS 17.6mo

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Clinical Question:

Can we replicate the successes reported in previous studies?

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Clinical Trial Objectives

- To evaluate bidirectional therapy for peritoneal metastasis
- Assess progression-free survival
- Evaluate ability to downstage patients to be eligible for HIPEC

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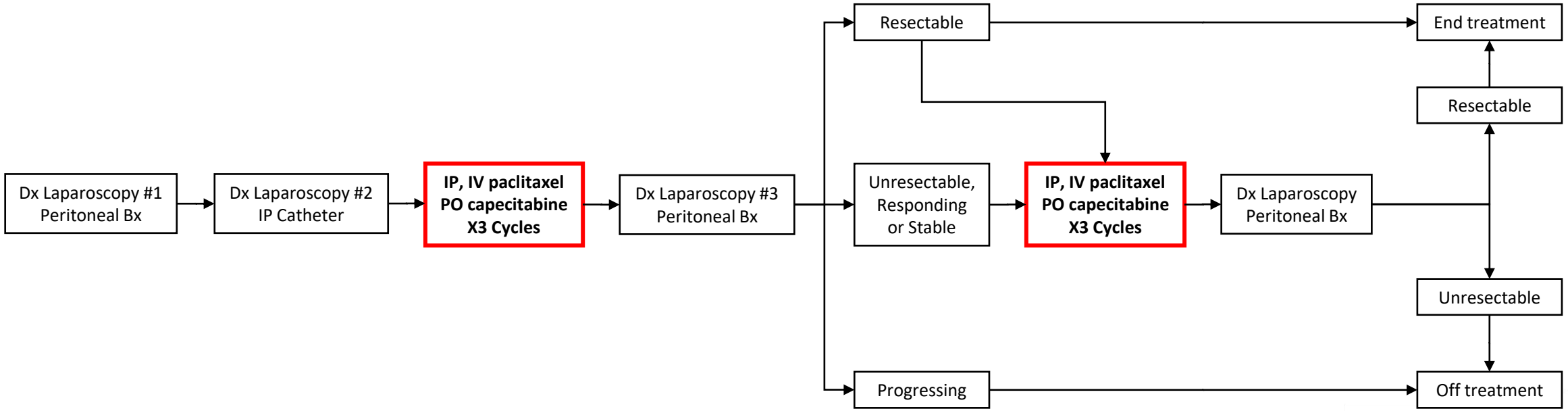
Protocol Design



Protocol Treatment

Chemotherapy Calendar

		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Cycles 1 and 4	**Week 1**	*,#	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Week 2	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Week 3	✓													
Cycles 2 and 5	**Week 4**	*,#	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Week 5	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Week 6	✓													
Cycles 3 and 6	**Week 7**	*,#	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Week 8	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Week 9	✓	Diagnostic laparoscopy, biopsies (between days 1 and 7)												

*** = IP paclitaxel; # = IV paclitaxel; ✓ = PO capecitabine**

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Inclusion/Exclusion Criteria

Inclusion:

- ≥18 years of age
- Confirmation of GE junction or gastric adenocarcinoma
- ECOG status ≤1

Exclusion:

- Extra-abdominal disease
- Allergy to therapeutic agent
- Prior intraperitoneal therapy
- Existing peripheral neuropathy

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Future Directions

- Dose-escalation studies of paclitaxel
- Evaluation of nab-paclitaxel (Abraxane®)
- Identify other IP/IV/PO drug combinations
- Exploration of early or adjuvant IP chemotherapy

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