Abbreviated Title: HIPEC for ACC

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Title: Phase II Trial of Surgical Resection and Heated Intraperitoneal Peritoneal Chemotherapy (HIPEC) for Adrenocortical Carcinoma

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Investigator Roles:

A. *Obtain information by intervening or interacting with living individuals for research purposes*
B. *Obtaining identifiable private information about living individuals*
C. *Obtaining the voluntary informed consent of individuals to be subjects*
D. *Makes decisions about subject eligibility*
E. *Studying, interpreting, or analyzing identifiable private*

information or data/specimens for research purposes

F. *Studying, interpreting, or analyzing de-identified data or specimens for research purposes*

G. *Some/all research activities performed outside NIH*

Commercial Agent: Cisplatin

PRECIS

Background:

- Adrenocortical carcinoma (ACC) is a rare tumor with an incidence of 1.5 to 2 per million people per year and has a very poor prognosis with an overall 5-year mortality rate of 75 - 90% and an average survival from the time of diagnosis of 14.5 months.
- The treatment of choice for a localized primary or recurrent tumor is surgical resection. For unresectable metastatic or recurrent disease, mitotane, aminoglutethimide, metapyrone, and ketoconazole are used.
- Cisplatin is one of the most effective chemotherapeutic agents for ACC. In the Surgery Branch we have conducted Phase I and II trials using heated intraperitoneal (IP) chemotherapy with cisplatin for primary peritoneal mesothelioma, low grade appendiceal adenocarcinoma, ovarian malignancies, and high grade adenocarcinoma of the gastrointestinal tract. Synergy has been demonstrated for cisplatin and hyperthermia
- The purpose of this trial is to determine if an aggressive surgical approach with intraperitoneal administration of heated cisplatin when tumor volume is minimal, can impact and improve on progression free survival.

Objective:

- To determine IP progression free survival after optimal debulking and heated IP chemotherapy with cisplatin in patients with IP spread of adrenocortical cancer

Eligibility:

- Histologically proven ACC evaluable by CT imaging with the majority of disease confined to the peritoneal cavity and surgically resectable to a residual size of less than 1 cm or amenable to radiofrequency ablation in patients who are > 18 years of age.

Design:

- This is a classic phase 2 trial to determine efficacy of this therapeutic strategy in ACC. Patients will undergo cytoreductive surgery to achieve a CCR of 0 or 1. Patients who are successfully debulked will then undergo HIPEC with cisplatin. Patients will be evaluated by associate investigators in coordination with the Principal Investigator for eligibility. Due to its exploratory nature, up to 30 patients may be enrolled to obtain 24 evaluable patients. (Patients must undergo successful debulking and HIPEC to be considered evaluable.)

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1.1.1 Primary Objective

- To determine intraperitoneal progression free survival after optimal debulking and heated intraperitoneal chemotherapy with cisplatin in patients with intraperitoneal spread of adrenocortical cancer

1.1.2 Secondary Objectives

- Determine morbidity of this procedure in this patient population
- Determine the impact of surgery and HIPEC on QOL
- Determine the impact of surgery and HIPEC on hormone excess
- Examine patterns of recurrence (local versus systemic)
- Perform molecular analyses to try to discern if there are intrinsic differences between tumors that recur widely throughout the peritoneal surface and those that metastasize to other organs or are confined to a local recurrence.
- Determine overall survival after optimal debulking and heated intraperitoneal chemotherapy with cisplatin in patients with intraperitoneal spread of adrenocortical cancer.

1.2 BACKGROUND AND RATIONALE

1.2.1 Adrenocortical Carcinoma

Adrenocortical carcinoma (ACC) is a rare tumor with an incidence of 1.5 to 2 per million people per year[1-3]. It has a very poor prognosis with an overall 5-year mortality rate of 75 - 90% and an average survival from the time of diagnosis of 14.5 months. Signs and symptoms due to excess hormonal secretion are seen in a large fraction of patients, further contributing to the morbidity associated with this disease.

The treatment of choice for a localized primary or recurrent tumor is surgical resection. Excisable primary tumors represent about 40% of cases at presentation; however, 60 - 80% of these patients eventually die from recurrent extensive metastases[4]. Patients with recurrent or metastatic disease are infrequently curable by surgery alone due to the propensity for intraperitoneal recurrence.

For unresectable metastatic or recurrent disease, mitotane, aminoglutethimide, metapyrone, and ketoconazole are used. Of these, mitotane is the only agent with both anti-tumor and adrenolytic effects. Aminoglutethimide, metapyrone, and ketoconazole are used to treat the symptoms of excess hormone production in patients with functional tumors. Mitotane, the most extensively studied agent, was reported to have response rates of 30-60% in older studies without standardized response criteria or the use of modern imaging technology[5-7]. Response rates of 20% or less have been noted with more modern imaging technology. These responses persist for an average of 10.5 months with no apparent impact on overall survival.

Most reports of cytotoxic therapy for ACC are anecdotal or include a small number of patients[8-13]. These studies report low response rates with the majority of responses classified as partial and

of less than one year in duration. Trials using mitotane in combination with various chemotherapeutic agents have had similar results[12, 13]. The largest randomized trial for metastatic or locally advanced ACC conducted was recently published and showed that a regimen of etoposide, doxorubicin and cisplatin (EDP) combined with mitotane was superior to the combination of stroptozocin and mitotane with a median PFS of 5.0 months vs. 2.1 months and response rate of 23.2 and 9.2% respectively[14].

A retrospective analysis was performed on fourteen patients with peritoneal predominant recurrences who were treated with EDP by Dr. Fojo's group at the NCI. Patients who did not respond to chemotherapy *survived an average of 14 months* following treatment; patients who demonstrated a response to the chemotherapy survived for an *average of 30 months*. While small, the numbers seem to indicate that response to chemotherapy may correlate with an increase in survival. Intraperitoneal chemotherapy allows the administration of high doses of chemotherapy directly to the tumor bed and thus may improve the progression free survival as well as overall survival in this patient population.

Dr. Fojo's group has also accumulated a large data base on metastatic adrenal cancer that includes whole exome sequence, as well as cDNA and microRNA array data. Preliminary data has shown a high level of expression of the chemokine receptor, CXCR4, on the membrane of adrenal cancer cells, and expression of the receptor's ligand, CXCL12 (SDF1) on the peritoneal surface. Because this finding may lead to a therapeutic option in the future, it will be further investigated during the course of this study as listed below.

1.2.2 Enumeration of Circulating Endothelial Cells (CEC)

Early increase of CEC following anti-angiogenic drug administration can be an interesting marker of treatment efficacy. Interpretation of CEC change must take into account multiple factors such as the mechanism of drug action, time of CEC measurement to drug administration, phenotype of CEC quantified. Theoretically, various antigens can be used to characterize mature CEC. In general CD45 expression is used to exclude hematopoietic cells, and CD133 to exclude immature cells. Commonly used endothelial markers include CD31, CD146, CD34, CD144 or CD105. However, there is a lack of consensus regarding combination of these markers to characterize CEC by flow cytometry analysis. In this study, we will evaluate pre- and post-treatment changes in mature circulating endothelial cells (CD 146+, CD133-), as determined by flow cytometry analysis. This evaluation will be conducted in Dr. Jane Trepel's lab, NIH/NCI/MOB. CEC may be collected (16ml in CPT blue/black tubes) pre surgery, at 6 weeks (+/- 2 weeks) and 6 months (+/- one month).

During the course of this study, tissue will be procured at the time of surgery and will undergo molecular analysis in order to try to discern if there are intrinsic differences between tumors that recur widely throughout the peritoneal surface and those that metastasize to other organs or are confined to a local recurrence.

1.2.3 HIPEC for ACC

Cisplatin is one of the most effective chemotherapeutic agents for ACC. In the Surgery Branch we have conducted Phase I and II trials using heated intraperitoneal chemotherapy with cisplatin for primary peritoneal mesothelioma, low grade appendiceal adenocarcinoma, ovarian malignancies, and high grade adenocarcinoma of the gastrointestinal tract. Synergy has been demonstrated for cisplatin and hyperthermia[15] and this was the basis for exploring the continuous

hyperthermic peritoneal perfusion with cisplatin in our initial Phase I trial. The dose-limiting toxicity in that trial was renal insufficiency related to systemic absorption of cisplatin and occurred at a dose of 350 mg/M2. All subsequent Surgery Branch trials using Cisplatin as the HIPEC agent were conducted using 250 mg/m2 with a thiosulfate bolus given 20 minutes before adding cisplatin to the intraperitoneal perfusate followed by continuous infusion of thiosulphate for an additional 12 hours.

We have used heated cisplatin in different histologies including primary peritoneal mesothelioma, low grade mucinous adenocarcinoma (including low grade mucinous neoplasms of borderline malignant potential), and adenocarcinoma of gastrointestinal tract origin however, the majority of our experience has been in intraperitoneal mesothelioma and low grade appendiceal adenocarcinoma. Phase II trials using cisplatin in both peritoneal mesothelioma and ACC have demonstrated some efficacy indicating potential similarity in the sensitivity of these histologies to cisplatin[9-12, 16-18]. In our studies, patients with peritoneal mesothelioma achieved an average PFS of 17 months[19] with younger age and completeness of resection being predictive of better outcomes.

1.2.4 Peritoneal carcinomatosis

Peritoneal carcinomatosis represents a formidable treatment challenge in oncology. Once considered a variant of systemic spread of disease, peritoneal carcinomatosis of most histologies is treated with palliative systemic chemotherapy alone, with surgery reserved only for palliation of disease- or treatment for related secondary events such as bowel obstruction and ascites. Systemic multi-drug chemotherapy has not altered the natural history of peritoneal carcinomatosis in more common diseases such as colorectal cancer, as patients suffer disease progression and functional deterioration due to visceral obstruction, malignant ascites and cancer cachexia over a matter of months[20-22]. The biology of peritoneal carcinomatosis is distinctive, unlike hematogenous metastasis. Insights into the natural history of peritoneal tumor dissemination have engendered novel multi-modality treatment approaches to this challenging clinical problem. Tumor dissemination across peritoneal surfaces occurs through established mechanisms of direct tumor extension; tumor cell spread in peritoneal fluid, and malignant peritoneal seeding from surgical manipulation of the tumor, and can occur in the absence of regional or distant nodal or systemic metastases.

Adrenal neoplasms are one of the most common of all human tumors[23]. The prevalence of adrenal incidentaloma is approximately 5% on abdominal imaging, but can be as high as 10% in the elderly. As the U.S. population ages, the management of adrenal incidentaloma will be an increasingly important issue in health care[23]. There are no reliable preoperative clinical, imaging or biochemical tests available to distinguish between primary benign and malignant adrenocortical neoplasms in the absence of obvious metastatic disease or locoregional invasion[24]. Imaging features such as tumor heterogeneity, irregular tumor border, hemorrhage, necrosis, rapid tumor growth rate, tumor Hounsfield unit >10-20 on non-contrast CT scan, and intravenous contrast washout of 40% or less after 15 minutes are more common in malignant tumors but are not reliable enough to avoid the need for adrenalectomy to exclude a cancer diagnosis nor to forgo continued follow up[24-29]. The majority of patients undergo laparoscopic adrenalectomy for diagnosis. ACC cannot be diagnosed by frozen section (postoperative histopathologic examination to distinguish between malignant and benign primary adrenal tumors is difficult) and thus peritoneal seeding from surgical manipulation is a particular problem with ACC as the procedure is performed without a tumor diagnosis[30, 31].

According to a recent publication, the rate of peritoneal carcinomatosis following laparoscopy is 30% at center experienced in laparoscopic procedures and 16% following open adrenalectomy. A European study suggests the 4 year rate of peritoneal carcinomatosis is 67% for laparoscopy and only 27% for open adrenalectomy. Due to increasing use of laparoscopy, this has evolved as a significant problem for patients with metastatic adrenocortical cancer. The clinical sequela is vexing as the peritoneum is a surface that is not well penetrated by traditional systemic intravenous chemotherapy. Hyperthermia alone has been shown to be toxic to malignant cells and we have previously combined cisplatin and hyperthermia in prior protocols safely.

1.2.5 Surgical metastasectomy

Surgical metastasectomy has been used extensively for ACC in our institution. Our published data and experience demonstrates the ability to safely perform this surgery and to prolong disease free interval to greater than a year in selected patients[32]. Combining surgery with Cisplatin, the drug most effective in ACC, seems like a logical direction for the treatment of this histology where the bulk of tumor is intraperitoneal. The purpose of this trial is to determine if an aggressive surgical approach with intraperitoneal administration of heated cisplatin when tumor volume is minimal, can impact and improve on progression free survival.

Given the aggressive treatment regimen and the aggressive nature of the diseases, it is important to understand the impact this therapy has on patients' health related quality of life. As a secondary endpoint we will therefore evaluate patients' health related quality of life prior to therapy and at intervals following recovery from the surgery and HIPEC. The goal of tracking quality of life is while surgery may temporarily negatively impact on QOL, it is our hope that it would rebound to better than pre-op if this approach has any merit and utility in the care of patients in the future.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

- Histologically proven ACC with the majority of disease confined to the peritoneal cavity and resectable or amenable to radiofrequency ablation
- Disease evaluable by CT or PET imaging
- All disease should be deemed resectable based on imaging studies e.g.:
    - Hepatic metastases (unilateral or bilateral ≤ 5 lesions, ≤ 15 cm total diameter)
    - **Note**: Hepatic lesions must be amenable to complete resection
    - Primary peritoneal metastases (small disease load ≤ P2 disease) without massive ascites or intestinal obstruction
    - Lung metastases (≤ 3 unilateral/bilateral, 9 cm total diameter)
    - **Note**: lung lesions must be amenable to complete resection
    - **Note**: Patients with both pulmonary and hepatic metastases will be enrolled at the discretion of the PI
    - **Note:** In situations where resection to Completeness of Cytoreduction Score (CC) 0 or 1 is uncertain, patients may undergo diagnostic laparoscopy prior to enrollment to determine feasibility of resection. (**Appendix D**)
- Greater than or equal to 18 years of age
- Able to understand and sign the Informed Consent Document

- Clinical performance status of ECOG ≤ 2
- Life expectancy of greater than three months
- Patients of both genders must be willing to practice birth control during and for four months after receiving chemotherapy
- Hematology:
    - Absolute neutrophil count greater than 1500/mm3 without the support of Filgrastim.
    - Platelet count greater than 75,000/mm3.
    - Hemoglobin greater than 8.0 g/dl.
- Chemistry:
    - Serum creatinine less than or equal to 1.5 mg/dl unless the measured creatinine clearance is greater than 60 mL/min/1.73 m2
    - serum AST and ALT within 5 times the upper limit of normal and a total serum bilirubin of less than 3 times the upper limit of normal, both of which define the upper limit of grade 2 treatment related toxicities.
    - PT within 2 seconds of the upper limit of normal (INR≤1.8)
- Recovered from any toxicity to grade 2 or less from all prior chemotherapy, immunotherapy or radiotherapy and be at least 30 days past the date of their last treatment with the exception of mitotane which may be continued.
- Able to understand their disease and the exploratory nature of combining surgery and HIPEC for this histology.

2.1.2 Exclusion Criteria

- Concomitant medical problems that would place the patient at unacceptable risk for a major surgical procedure.
- History of congestive heart failure and/or an LVEF < 40%
- **Note**: Patients at increased risk for coronary artery disease or cardiac dysfunction (e.g., >65yo, diabetes, history of hypertension, elevated LDL, first degree relative with coronary artery disease) will undergo full cardiac evaluation and will not be eligible if they demonstrate significant irreversible ischemia on stress thallium or an ejection fraction <40%.
- Significant COPD or other chronic pulmonary restrictive disease with PFT's indicating an FEV1 less than 50% or a DLCO less than 40% predicted for age
  Note: Patients who have shortness of breath with minimal exertion or who are at risk for pulmonary disease (e.g., chronic smokers) will undergo pulmonary function testing and will not be eligible if their FEV1 is < 50% of expected.
- Grade 2 or greater neuropathy
- Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the chemotherapy on the fetus or infant.
- Brain metastases or a history of brain metastases
- Childs B or C cirrhosis
- Evidence of severe portal hypertension by history, endoscopy, or radiologic studies
  Note: Any diagnosis of portal hypertension or clinical stigmata of such including but not limited to gastric or esophageal varices, umbilical vein varices or telangectasias.
- Weight < 30 kg

- Active systemic infections, coagulation disorders or other major medical illnesses of the cardiovascular, respiratory or immune system, myocardial infarction, cardiac arrhythmias, obstructive or restrictive pulmonary disease

2.2 SCREENING EVALUATION

2.2.1 Within 6 weeks prior to treatment:

- HIV, Hepatitis B surface antigen and Hepatitis C antibody
- 12 lead EKG
- Patients will undergo pulmonary function tests as indicated in section **2.1.2**
- Cardiac evaluation with possible stress test for patients with history of cardiac disease will be performed as indicated in section **2.1.2**
- ECHO if prior history of doxorubicin
- Thoracic oncology consult for patients with pulmonary metastatases
- Confirmation of pathology by the NCI Laboratory of Pathology [may be completed any time prior to enrollment]
- Radionuclide bone scan, when clinically indicated
- MRI Brain when indicated
- PET-CT when indicated

2.2.2 Within 4 weeks prior to treatment

- Baseline imaging: CT scan of chest, abdomen and pelvis (CT C/A/P) with triphasic 1mm cuts as per the liver scan protocol. For patients with evidence of hepatic disease, a baseline MRI-L will be performed.
- Completion of Health Related Quality of Life Forms (HRQOL)

2.2.3 Within 2 weeks prior to treatment

- Complete history and physical examination including vital signs, height and weight as well as ECOG assessment.
- Laboratory evaluation
    - CBC with platelets
    - Chem-20 (Sodium (Na), Potassium (K), Chloride (Cl), total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LD, Total Protein, total CK,
    - C-reactive protein, Hg A1c, Ferritin, Prealbumin,
    - PT/PTT & INR,
    - Urinalysis
- Tumor markers as indicated (serum cortisol, 24 hour urine for cortisol, ACTH, DHEA, and LDH)
- Anesthesia consult

2.2.4 Within 1 week of surgical treatment:

- Beta HCG for women of child bearing potential

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 10days of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.4 STRATIFICATION PROCEDURES

Patients will be stratified in to 2 groups: those with peritoneal recurrence only and those with visceral metastatic disease.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a classic phase 2 trial to determine efficacy of this therapeutic strategy in ACC. Patients will undergo cytoreductive surgery to achieve a CC of 0 or 1. Patients who are successfully debulked will then undergo HIPEC with cisplatin. Patients will be evaluated by associate investigators in coordination with the Principal Investigator for eligibility. Due to its exploratory nature, up to 30 patients may be enrolled to obtain 24 evaluable patients. (Patients must undergo successful debulking and HIPEC to be considered evaluable.)

NIH Advanced Directives Form:

As indicated in section **9.3**, all subjects will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required

Surgical Guidelines:

Note: The following guidelines are for the purpose of promoting consistency in the surgical procedure and perioperative care where possible. Physician discretion will be exercised as necessary to ensure that the specific needs of the patient are met. Details pertaining to surgical and perioperative management will be recorded in the patient medical record; only variables specified in section **6** will not be captured on the CRFs.

3.2 PREOPERATIVE PATIENT MANAGEMENT

Patients will receive standard preoperative care as appropriate to the planned surgical intervention and the patient's underlying health status which may include:

- The day prior to surgery: Sequential Compression Devices (SCDS), incentive spirometry and appropriate bowel preparation regimen, and hydration
- The night before operation: Hibiclens® shower
- Beginning the night prior to the operation, the patients will be hydrated intravenously in preparation for the HIPEC with cisplatin.

Note: For patients undergoing hepatic resection, no anticoagulation will be given prior to operation. For patients receiving an epidural catheter heparin will not be given until the catheter has been successfully placed.

3.3 PATIENT MANAGEMENT IN THE OPERATING ROOM

- Patients will receive perioperative antibiotics and the first dose will be administered prior to incision.
- Epidural catheters should be considered in all patients. Decisions will be made by the anesthesiologist and the operating surgeon in full collaboration.
- SCDs will be "on" before induction of anesthesia.
- A central venous line, arterial line, and large bore catheters will be placed if blood loss is anticipated to be >500cc or at the discretion of the anesthesiologist in consultation with the surgeon.

3.4 PERITONEAL METASTASECTOMY AND CYTOREDUCTIVE SURGERY

- If there is evidence that the extent of disease is beyond the ability to be cytoreduced such that the largest residual tumor nodule is $\geq$ 1.0 cm, patients will not be considered for intraperitoneal cisplatin.
- For patients with primary peritoneal metastases without massive ascites or intestinal obstruction, all visible disease will be resected if technically feasible.
- Peritonectomy for patients with peritoneal disease includes the following: the right and left sub-diaphragmatic peritoneum, the falciform ligament, lesser and greater omentum, anterior, right and left abdominal wall down to the paracolic gutters and the pelvic peritoneum.
- Partial (limited) peritonectomy for patients with intra-abdominal disease without peritoneal disease includes (i.e., liver metastases without peritoneal disease): peritoneal attachment of the hepatic left lateral segment and the spleen, 2 cm along the incision at the anterior abdominal wall and the falciform ligament
- Organs may be resected en bloc if invaded by tumor. For example, the spleen is often involved in recurrent tumors from a left sided primary. Organs that may be resected include but are not limited to colon, small bowel, pancreas, spleen, and liver.
- If a colonic anastomosis is required, a diverting ileostomy will be performed. This will be reversed after appropriate healing of the anastomosis.
- After the cytoreduction has occurred and the patient is either a CCR 0 or CCR 1 then cisplatin heated intraperitoneal infusion will be conducted for 90 minutes at goals of at least 40°C.

3.5 INTRAPERITONEAL CHEMOTHERAPY HIPEC

- Perfusion
    - Two large bore catheters will be inserted through the abdominal wall, one over the right lobe of the liver and one in the pelvis. The abdominal fascia will be closed, and the catheters connected to a perfusion circuit.
    - The perfusion flow rate will be maintained at approximately 1.0 L/min as tolerated and a perfusate volume will be maintained which moderately distends the abdominal cavity this volume will vary depending on the amount of ascites in any given patient.

- Stable perfusion parameters are obtained and the peritoneal cavity is warmed to a minimum of 40° C prior to starting the clock for perfusion time.
- The perfusion will be continued for 90 minutes.
- During the perfusion, constant physical manipulation of the abdomen (shaking) will be maintained for the entire time to assure even distribution of the perfusate.
- Peritoneal temperature will be measured continuously by three probes placed immediately beneath the peritoneal surface on either side of the abdomen and in the pelvis.
- The patient's core temperature will be measured with an esophageal probe (which correlates well with pulmonary artery temperatures) and maintained at less than 41°C using a cooling blanket and ice packs as needed.
- At the end of the perfusion, the abdomen will be re-opened and the perfusate irrigated from the abdominal cavity.

3.6 MEDICATIONS

- Cisplatin will be calculated on ideal body weight (IBW). Ideal body weight will be calculated based upon the following formula:

  IBW (male, in kg) = [(Height in inches – 60) x 2.3] + 50

  IBW (female, in kg) = [(Height in inches – 60) x 2.3] + 45.5

- Cisplatin 250mg/m2 will be diluted in 1 liter of 0.9% sodium chloride for injection as described in Section 11.1.3
- Sodium thiosulfate.
  - In order to limit the systemic toxicity of cisplatin, sodium thiosulfate will be administered by continuous intravenous infusion starting immediately prior to the perfusion and continuing for a total of 12 hours.
  - A loading dose of 7.5 gm/M2 of sodium thiosulfate will be diluted in 150 cc of 0.9% sodium chloride for injection. This loading dose will be infused over 20 minutes beginning with the addition of cisplatin to the peritoneal perfusion circuit.
  - Immediately following this bolus dose an additional 25.56 gm/M2 of sodium thiosulfate will be diluted in 1000 cc of 0.9% sodium chloride for injection for a maintenance infusion of 2.13 gm/M2 per hour for 12 hours. The maintenance infusion will be delivered over 12 hours by Infusion Pump.

3.7 POST-OPERATIVE CARE

3.7.1 Patient Monitoring

- The patients will be monitored in the Intensive Care Unit for no less than 12 hours after surgical resection. Routine ICU monitoring of vital signs will be performed according to the patient's clinical status. While in the ICU, an attempt to keep urine output greater than 100cc/hour will be made when physiologically feasible until the sodium thiosulfate is completed.
- Patients will be discharged from the ICU at the discretion of the treating surgeon and in accordance with the institution policies.
- Following discharge from the ICU, vital signs (blood pressure, temperature, pulse, respirations) will be taken per routine (every 2-6 hours and as clinically indicated).
- Patients will receive routine post-operative care; early ambulation will be encouraged.

- Laboratory evaluations will include:
  - CBC, platelets, acute care, mineral and hepatic panel daily x 4 days and then every third day or as clinically indicated until discharge.
  - Tumor markers for new baseline will be obtained on the day of discharge as indicated.
- Other evaluations
  - Imaging studies as clinically indicated.

3.8 Research Evaluations

- Circulating endothelial Cells may be collected - 16ml in CPT blue/black tubes
  - Within 1 month prior to surgery
  - 6 weeks (+/- 2 weeks) post surgery
  - Every 6 months (+/- one month) post surgery
- Blood will be transported to:

Jane Trepel - Cell Signaling Lab
Room10/12n230
301-496-1547

3.9 Discharge

- Total hospitalization may be approximately 7-14 days.
- Patients who are discharged within this time frame should be able to tolerate an oral diet. Patients who have a prolonged hospitalization but are able to tolerate a diet may be discharged with home rehab/physical therapy.

3.10 Post Discharge

- CBC weekly following discharge or until toxicities have resolved (less than grade 3 or baseline) and patient has recovered from nadir. This may be done through the patient's referring physician with the results faxed to Dr. Hughes or her designee.
- Patients will return to clinic approximately 4-8 weeks following surgery for their 1st post- operative visit and will be followed as clinically indicated until recovery. Upon recovery from the surgical procedure, the following end of treatment evaluations will be performed:
  - Imaging studies to establish new baseline
  - Tumor markers as indicated
  - CBC, acute care, mineral and hepatic panel, CRP, Albumin, pre-albumin, ferritin, Hgb A1c if elevated pre-op.
  - Physical examination to include ECOG, weight and vital signs
  - QOL survey

3.11 Treatment Assessment and Response (Follow up period)

- Because of the nature of peritoneal imaging and because cytoreductive surgery will likely eliminate all imageable disease, response can only be measured in terms of radiographic disease-free survival. At any time point when there is evidence of progressive disease (imageable tumor nodules or increasing ascites persistent on CT scans as interpreted by the official interpretation of the imaging studies) the patients will be scored as progressive disease. In some cases this may require successive scans, but the time of

recurrence will be retrospectively defined at the point the first scan demonstrated imageable disease.

- Patients will be evaluated 3 months from the operative date (+/- 1 month) intervals for the first year; every four months for (+/- 1 month) the next year and then q 6 months (+/- 1 month) thereafter.
- The following evaluations will be performed at each visit:
    - Imaging studies
    - Physical examination to include ECOG, weight and vital signs
    - Tumor markers as indicated
    - CBC, acute care, mineral and hepatic panel, CRP, Albumin, pre-albumin, ferritin, Hgb A1c if elevated pre-op.
    - Completion of Health related Quality of Life Forms (HRQOL) – at the first follow up visit and then at each evaluation until off study.
- Patients who are unwilling or unable to return for follow up evaluation will be followed every 6 months by phone contact until off study criteria are met. The following information may be obtained:
    - Summary of treatment received since the previous contact
    - Estimation of ECOG status
    - Request for imaging studies, physical exam and laboratory reports to be sent to the PI

Note: if patient is taken off study prior to 1 year following surgery, the HRQOL will be completed at the off study evaluation if possible.

3.12 Measurement of Health Related Quality of Life

Baseline Quality of Life Questionnaires (QOL) will be completed prior to the surgical procedure during the first follow up visit [following recovery from the surgical procedure] approximately one year following the procedure or at the time off study.

Patients will be informed of the details of the QOL part of this study and reassured that their decision to participate will not affect their participation in the protocol. Once enrolled, the patient has the right at any time to elect not to continue completing the questionnaires. In the event a patient goes off study prior to completion of the follow up time points, the data gathered from their completed QOL questionnaires will be included in the final analysis.

Measures will be initially administered by the Associate Investigator Research Nurse or designee prior to randomization. The Research Nurse will assess the patient's ability to read, and if the patient is unable to read, it will not be administered. The Research Nurse or designee will administer the questionnaires providing a firm surface at a table or a clipboard and a pencil. The patients will be directed to complete the questionnaires using the following instructions:

We would like to better understand how you and other persons in this study feel, how well you are able to do your usual activities, and how you rate your health while you are participating in this research study. To help us better understand these things about you and other persons participating in this study please complete this questionnaire about your quality of life. This questionnaire should not take longer than 15 minutes to complete.

The questionnaire is simple to fill out. Be sure to read the instructions on the top of the questionnaire. Remember, this is not a test and there are no right or wrong answers. Choose

the response that best represents the way you feel. I will quickly review the questionnaire when you are done to make sure that all the items have been completed. Please answer all the items with the response that is most applicable.

You should answer these questions by yourself. Your husband/wife or other family members or friends should NOT assist you in completing the questionnaire. Please fill out the questionnaire now. Return the questionnaire to me when you have completed it. We will be asking you to complete this again during some of your follow up visits. If you have any questions, please ask.

Once the patient has completed the questionnaire, the Research Nurse or designee, will review it for completeness and thank the patient for their cooperation. Subsequent measurements will be administered by the Associate Investigator Research Nurse, or designee, when the patient returns for follow-up visits as specified in section **3.11**.

The Research Nurse or designee will request that the patient complete the questionnaire prior to seeing the physician, as the interaction between the patient and physician may influence the patient's answers to the questionnaire. In the event a patient is taken off study, patients will be asked to complete one last questionnaire (as appropriate to the point of withdrawal) and the data will be included in the analysis.

3.13 Criteria for Removal from Protocol Therapy and Off Study Criteria

Prior to documenting removal from protocol therapy, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.13.1 Criteria for removal from protocol therapy

- Inability to undergo HIPEC
- Unwilling to comply with treatment regimen or prescribed follow-up
- Completion of treatment phase
- Positive pregnancy test

3.13.2 Off Study Criteria

- Death
- Disease progression requiring systemic therapy
- Start of any therapeutic agent other than mitotane
- Completed study follow-up period
- Participant requests to be withdrawn from the study
- Lost to follow up
- PI decision to close the study

3.13.3 Off Protocol Therapy and Off Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

During the post-operative period, patients will receive all standard of care supportive measures including possible nasogastric tube drainage and bowel rest for ileus, pulmonary toilet teaching and incentive spirometry to prevent atelectasis, transfusions, and antibiotics as indicated.

5 BIOSPECIMEN COLLECTION

No specimens will be collected for future research purposes on this protocol. Patients who are willing to have specimens collected for future research purposes will be co-enrolled on protocol 13-C-0176.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

Data will not be distributed outside NIH without IRB notification.

Dr. Hughes will continue to have access to the data for purposes of data analysis and publication when she is at Eastern Virginia Medical. She will also have access to the data via a secure flash drive. It is also possible that data will be sent to her via encrypted email. Dr. Hughes' involvement in this research is covered under the Federal Wide Assurance of the NIH.

6.2 ROUTINE DATA REPORTING

6.2.1 Laboratory events will be captured as follows

- During hospitalization for surgical resection, only the admission labs, first morning labs drawn after 4am, and labs that support the diagnosis of a reportable event will be uploaded into C3D.
- For laboratory values obtained at sites other than the NIH Clinical Center: only the following values (highest grade per cycle) will be captured in C3D:
    - Hemoglobin, total white blood cell count, absolute neutrophil count, platelet count
    - PTT, PT or INR
    - Creatinine, ALT, AST, Bilirubin (total and direct),
    - Any unexpected laboratory abnormality ≥ grade 2 possibly, probably or definitely related to the research

6.2.2 Concomitant Measures and Medications

- Only those medications that the patient is taking at baseline on a routine basis or medications that cause an AE will be captured in C3D. [Thus onetime medications, PRN medications, and medications given to treat adverse events will not be captured in C3D.]
- Vital signs will be captured once at baseline
- Evaluations that are performed for clinical indications only will not be captured (e.g. daily chest x-rays during hospitalization, interim post op visits)

6.3 ADVERSE EVENTS

All adverse events will be described in the source documents

6.3.1 The following adverse events of any grade will be captured in C3D:

- Abscess formation
- Fistula formation
- Length of Stay (LoS) >14 days (LoS is defined as the time in days from the date of the procedure until the date that discharge criteria are met).

NOTE: If the discharge criteria date is not the same as the actual date of discharge, the date the patient met discharge criteria should be documented in CRIS.

6.3.2 Exclusions to Routine Adverse Event Reporting

The following Adverse Events will be captured only in the source documents and will not be reported in C3D.

- For the duration of the study
  - Laboratory values that do not support the diagnosis of a reportable event with the exception of noted events in section **6.3.2**.
  - All grade 1 events
- During hospitalization for surgical resection
  - Grade 1 and 2 events
  - Grade 3 and 4 events which resolve during the first 72 hours following surgery
- Post-operative recovery phase (following discharge)
  - Grade 1 and 2 events
  - Events that result in a hospitalization for convenience will not be reported.
- During the follow up period (more than 30 days following the last treatment)
  - Only those events that are serious, unexpected, and related to the treatment will be captured in C3D.

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical

examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section **6.3.2**.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per section **7.2**.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Note: Events that result in a hospitalization for convenience will not be reported.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB approved research protocol.

7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; AND
- Is related or possibly related to participation in the research; AND
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NCI-IRB AND CLINICAL DIRECTOR REPORTING

7.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance

3. A tabular summary of the following adverse events:
    - All Grade 2 unexpected events that are possibly, probably or definitely related to the research;
    - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
    - All Grade 5 events regardless of attribution;
    - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported

7.3 DATA AND SAFETY MONITORING PLAN

7.3.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 STATISTICAL CONSIDERATIONS

The primary objective of this trial is to conduct a pilot study to determine if the use of debulking surgery and HIPEC in patients with intra-peritoneal spread of adrenocortical carcinoma is able to be associated with an intra-peritoneal progression free interval which may exceed that of the use of chemotherapy alone.

Data from a recently published study indicated that a 5.0 month median PFS[14] may be attained in similar patients using EDP and mitotane. This will be a single arm trial with the goal of seeing if the proposed combination of HIPEC and surgery may be associated with a 10 month median PFS. Using the method of Brookmeyer and Crowley[33], the study will plan to enroll 24 fully evaluable patients over a 60 month period. Based on this method, with 24 subjects, there would be 80% power to determine if there is a median PFS of 10 months rather than 5 months, based on a one-tailed 0.10 alpha level test. In practice, Kaplan-Meier curves and appropriate confidence intervals at selected time points will be provided to help interpret the results relative to historical results.

At the rate of 6 patients per year, 24 evaluable patients could be enrolled in 5 years, allowing for a ceiling of 30 patients to account for patients who may be inevaluable.

9 HUMAN SUBJECTS PROTECTION

9.1 RATIONAL FOR SUBJECT SELECTION

The investigational nature and objectives of this trial, the procedure and the treatments involved, the attendant risks and discomforts, potential benefits and potential alternative therapies will be carefully explained to the patient in the clinic setting and in the hospital prior to treatment and prior to obtaining a signed Informed Consent. This is particularly important for this study because of the relatively unique nature by which the treatment is given. That is to say, the patients must subject themselves to a major operative procedure with the attendant risks and complications associated with it in order to receive treatment without any assurance of benefit from the treatment.

9.2 PARTICIPATION OF CHILDREN

The surgical regimen used in this protocol is a major procedure which entails serious discomforts and hazards for the patient, such that fatal complications are possible. It is therefore only appropriate to carry out this experimental procedure in the context of life threatening adrenocortical carcinoma. Since the efficacy of this experimental procedure is unknown, it does not seem reasonable to expose children to this risk without further evidence of benefit. Should results of this study indicate efficacy in treating adrenocortical carcinoma, which is not responsive to other standard forms of therapy, future research can be conducted in the pediatric population to evaluate potential benefit in that patient population.

9.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **9.5**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MAS Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

9.4 EVALUATION BENEFITS AND RISKS/DISCOMFORTS

The potential benefit to patients undergoing this therapy would be palliation in terms of preventing or delaying intra-abdominal tumor progression and metastases elsewhere which can be a devastating and painful source of symptoms and cause for demise. In addition, significant tumor response may extend progression free and overall survival. The risks for this protocol include the risks associated with any abdominal surgery. This includes postoperative bleeding, intra-abdominal infection, enterocutaneous fistulas, anesthetic mishap and perioperative death. In addition, the toxicities of chemotherapy place the patients under risk. A combination of surgery and chemotherapy may decrease healing at a time when healing of abdominal wounds and bowel anastomosis is essential for recovery. All attempts will be made to avoid

enterotomies or a bowel resection where feasible. In the case of intra-abdominal catastrophe after surgery, patients may require reoperation.

9.5 Risks/Benefit Analysis

Patients with peritoneal carcinomatosis suffer with recurrent bowel obstructions, nausea, vomiting, crampy abdominal pain and incapacitating ascites. This clinical scenario justifies aggressive treatment strategies as a means of palliation and survival benefit. In Phase I and II trials we have seen long-term remissions after HIPEC in patients who were otherwise terminal with no other therapeutic options available.

The potential benefit is great for these patients if a regional response is obtained.

There is a direct benefit to patients to stay on study during the follow up period because we follow them for disease recurrence. If or when we identify disease recurrence, we are often able to facilitate treatment, either on an NCI investigator protocol, or by referring to a colleague that treats the same disease process.

Therefore, this protocol involves greater than minimal risk, but presents the prospect of direct benefit to individual subjects.

9.6 Consent Process and Documentation

All patients are thoroughly screened prior to initial consultation at the NIH. This usually involves a telephone conversation between the patient and a physician or nurse associate investigator. During the initial consultation the patient, along with family members, is presented a forthright and detailed overview of the treatment option available to them at the NIH. The experimental nature of the treatment, its theoretical advantages and disadvantages, and an overview of the operative procedure and anticipated convalescence are presented. The fact that the patient may undergo an operative procedure in order to receive therapy without any assurance of benefit, the aggressive nature of the treatment, and the likelihood of serious or potentially life-threatening complications are presented. The Informed Consent document is given to the patient and they are asked to review it, make notes and follow-up with a phone call to the physician or nurse investigator to have any additional questions answered prior to considering treatment on protocol.

When the patient is admitted to the Clinical Center for treatment, an associate physician investigator responsible for the care of the patient presents the previously described information in detail. The research nurse or Principal Investigator, or designee is responsible for obtaining consent from the patient upon admission. The patient is reassured that participation on the trial is entirely voluntary and that they can withdraw or decide against treatment at any time without adverse consequences. In fact, the investigators assure the patient that if alternate therapies are preferred that we will do all that we can to facilitate obtaining consultation and treatment from the appropriate medical center. The signed consent will be verified by the physician responsible for the care of the patient. The patient is asked to participate in completing the self-administered questionnaires measuring health related quality of life during this study. They are assured that their eligibility to participate in the perfusion portion of this study is not dependent upon their willingness to complete the quality of life questionnaires.

9.6.1 Re-consent via telephone

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

9.6.2 Informed consent of non-English speaking subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, and OHSRP SOP 12, 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

10 PHARMACEUTICAL INFORMATION

10.1 CISPLATIN (CDDP)

10.1.1 Source

Cisplatin is commercially available as a white lyophilized powder in 10cc and 50cc vials with mannitol and sodium chloride (Platinol, Bristol-Myers, Squibb, Princeton, NJ). It will be purchased from commercial sources by the NIH Clinical Center Pharmacy Department.

10.1.2 Stability/Storage

After reconstitution with water for injection, USP, to a concentration of 1 mg/mL, cisplatin is stable at controlled room temperature ($24^0C + 2^0C$) at 37^0C, and at 60^0C for at least 14 days. Further dilution at 0.05 or 0.5 mg/mL with 0.9% sodium chloride injection (NS), USP, yields a solution that is stable for at least 24 hrs at room temperature. Intact vials in reconstituted solution should be maintained at room temperature.

10.1.3 Preparation

Vials containing 10 and 50 mg of cisplatin will be reconstituted with 10 and 50 cc water for injection, USP, respectively to a concentration of 1 mg/mL. The total dose of cisplatin will be injected into a bag of 0.9% sodium chloride for injection, USP, to make 1 liter of final volume (± 10%) prior to administration.

10.1.4 Administration

Cisplatin at a dose of 250 mg/M2 will be added to a stable perfusion system at a flow rate of 1.5 - 2 L/min after draining an equivalent volume.

10.1.5 Toxicities

Cisplatin produces renal tubular toxicities associated with renal insufficiency and electrolyte, (i.e. magnesium, potassium, calcium, phosphate, bicarbonate) wasting which may result in significant hypomagnesemia and hypokalemia. Neurotoxicity manifests as both sensory and motor peripheral neuropathies. Cisplatin is also toxic to the 8th cranial nerve producing ototoxicity which consists primarily of deficits in high frequency auditory acuity, but may include vestibular abnormalities. Systemic administration of cisplatin at doses similar to those planned in this study are associated with significant nausea and vomiting and bone marrow suppression, particularly leukopenia and thrombocytopenia. Transient moderate elevations of hepatic transaminases, (i.e. AST, ALT) and acute systemic allergic reactions including anaphylaxis may also occur. The prior Phase I study of CHPP with cisplatin has not identified any regional intraperitoneal toxicity from cisplatin. The dose limiting systemic toxicity was renal toxicity at doses of 350 mg/M2. No other systemic toxicities were identified at that dose level.

10.2 SODIUM THIOSULFATE

10.2.1 Formulation

Sodium thiosulfate injection, USP, is commercially available as a sterile nonpyrogenic solution of sodium thiosulfate dissolved in water for injection, USP, at concentrations of 10% (100 mg/mL) at 25% (250 mg/mL). The commercial formulation may also contain boric acid and sodium hydroxide to adjust the pH to 8.5 - 9.0. It will be purchased commercially by the NIH Clinical Center Pharmacy Department.

10.2.2 Stability/Storage

The commercial formulation bears the manufacturer's expiration date.

10.2.3 Preparation

A loading dose of 7.5 gm/M2 of sodium thiosulfate will be diluted in 150 cc of 0.9% NS. An additional 25.56 gm/M2 will be diluted in 1000 mL 0.9% sodium chloride for injection for maintenance infusion.

10.2.4 Administration

Sodium thiosulfate will be given as an i.v. loading dose of 7.5 gm/M2 body surface area over 20 minutes followed immediately by continuous i.v. maintenance infusion of 2.13 gm/M2/hr for 12 hours delivered by IMED infusion pump. The loading dose of sodium thiosulfate will be started immediately prior to beginning intraperitoneal CDDP administration.

10.2.5 Toxicities

Other than osmotic disturbances, sodium thiosulfate is well tolerated in humans. Large orally administered doses are associated with a cathartic effect. In preclinical studies in dogs continuous i.v. administration of sodium thiosulfate has produced hypobilemia presumably due to an osmotic diuretic effect.

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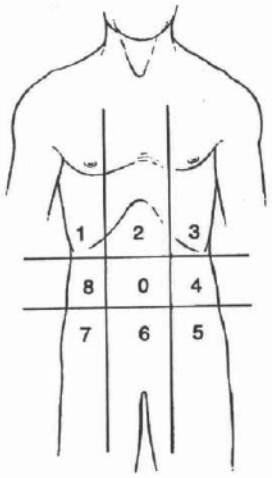
Ref Type: Generic

12 APPENDICES

12.1 APPENDIX A: PERITONEAL CANCER INDEX

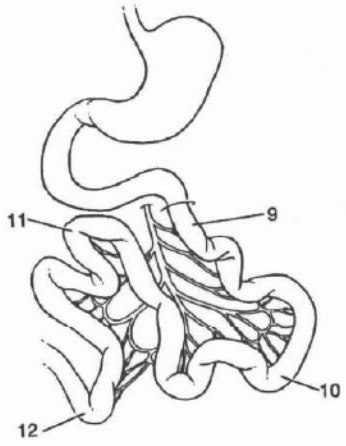
Peritoneal Cancer Index



Regions	Lesion Size
0 Central	____
1 Right Upper	____
2 Epigastrium	____
3 Left Upper	____
4 Left Flank	____
5 Left Lower	____
6 Pelvis	____
7 Right Lower	____
8 Right Flank	____
9 Upper Jejunum	____
10 Lower Jejunum	____
11 Upper Ileum	____
12 Lower Ileum	____
PCI	☐

Lesion Size Score

LS 0 No tumor seen
LS 1 Tumor up to 0.5 cm
LS 2 Tumor up to 5.0 cm
LS 3 Tumor > 5.0 cm or confluence



12.2 APPENDIX B: ECOG PERFORMANCE STATUS

Grade ECOG Performance

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled -cannot carry on any self-care. Totally confined to bed or chair
5	Dead

12.3 Appendix C: Health Related Quality of Life

The Functional Assessment of Cancer Therapy-Colorectal is a 36 item Likert-type survey of 27 general questions divided into four domains (physical well-being [7 items], social/family well-being [7 items], emotional well-being [6 items], and functional well-being [7 items]) appropriate for use with patients with any form of cancer and a cancer subscale of 9 questions specific for colon cancer or patients experiencing abdominal symptoms. The time frame on which responses are based is "during the past seven days". The tool takes approximately 10 minutes to complete. Total score and specific subscale scores can be analyzed. The reliability of the FACT-C demonstrates an alpha coefficient of 0.89, an overall test-retest reliability of .92. Concurrent validity is supported by a strong correlation with the Functional Living Index-cancer (FLIC) 0.80 and the self-administered version of the Quality of Life Index (QLI) 0.74. Since this study will be measuring changes in quality of life over time in response to the cancer therapy, the selected tool must be sensitive to change. The FACT-C has been analyzed correlating patient-reported performance ratings. One way analyses of variance indicated an acceptable level of sensitivity to change.

12.4 APPENDIX D: COMPLETENESS OF CYTOREDUCTION SCORE

CC-0 All visible tumors are removed during cytoreduction surgery, and there is no visible cancer in the abdomen at the completion of the surgery

CC-1 Tumor nodules remain in the abdomen or pelvis after surgery but are less than 2.5mm in size

CC-2 Tumor nodules remain in the abdomen or pelvis and are between 2.5 mm and 2.5 cm in size

CC-3 Tumor nodules greater than 2.5 cm of a confluence (merging) of non-removable tumor nodules remain at any site in the abdomen or pelvis after surgery