2009-0528: A phase II study of hyperthermic peritoneal perfusion (HIPEC) for adolescent and young adults with desmoplastic small round cell tumor (DSRCT) and other non-carcinomas

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Background

Extensive peritoneal disease or peritoneal carcinomatosis represents an aggressive mode of spread for many tumors which ultimately results in death. In most cases progression of the intraperitoneal disease precedes distant metastasis and patients typically die of complications related to the intraperitoneal disease. There is no standard chemotherapy which has shown promise in the treatment of peritoneal carcinomatosis for adults or children. The extent of retroperitoneal disease can limit complete surgical resection and the intensive post-operative chemotherapy regimens are only useful if a complete response (CR) is evident. For sarcomatosis as is found in desmoplastic small round cell tumor (DSRCT), if residual disease is present there have been no survivors after intensive chemotherapy even with stem cell rescue. (1) This may be related to the difficulty in obtaining cytotoxic concentrations of chemotherapy within the tumor parenchyma. A regional approach to treating the intraperitoneal tumor is appealing as a means of delivering high concentrations of chemotherapeutic agents directly to the tumor while limiting systemic toxicity. (By means of using the peritoneal surface as barrier to systemic absorption) (2) This approach has been demonstrated to be very effective for advanced ovarian cancer, appendiceal carcinoma and has become the standard care for adults in many cancer centers. (3) In phase I and II clinical trials, this strategy has also been found to improve disease free survival in mesothelioma and gastric cancer. (4-6)

DSRCT primarily presents in children and young adults age 5-30, 90% male, with dozens to hundreds of abdominal tumor implants. Less than 200 cases are reported in the world literature and therefore treatment options are limited. Despite chemotherapy, aggressive tumor debulking and radiotherapy, 3 year survival is 20-30%. After aggressive tumor debulking of Desmoplastic round cell tumor (DSRCT), various strategies have been employed which direct therapy toward the peritoneal disease because of the characteristic loco-regional pattern of spread. Such approaches have included intraoperative radiation therapy (IORT) and hyperfractionated radiation therapy. (7-10) Some chemotherapy and radiation responses have been documented, but local abdominal recurrence shortly follows. While these approaches attest to the acknowledged importance of controlling intra-abdominal disease, they have not been uniformly successful in the long term complications of secondary tumors. (11-13)

Other rare pediatric tumors which can recur and metastasize in the abdominal cavity include Wilms' tumor, colon carcinoma, sarcoma, and malignant ovarian germ cell tumor. With advanced intraperitoneal disease, these tumors are usually fatal despite aggressive chemotherapy and radiation therapy. In a novel approach to these aggressive tumors, here at UT MDACC, an investigator initiated phase I study found that continuous hyperthermic peritoneal perfusion, also known as HIPEC, is safe in children.

HIPEC is a technique for combining hyperthermia and chemotherapeutic agents delivered intraoperatively to the peritoneal and retroperitoneal surface via a recirculating perfusion circuit. (14) In addition to adult clinical trials, the support for this concept comes from in vivo and in vitro laboratory studies. The selective lethal effect of supranormal temperatures on human and murine neoplastic cells has been well established in laboratory models. (15-17) A variety of cell lines including colon carcinoma and melanoma have been shown to be sensitive to temperatures ranging from 42 to 45°C when exposed for a period of 2 to 4 hours while their non-neoplastic parental cell types are largely unaffected. In vivo, there appears to be a differential

response of normal and tumor microcirculation in response to hyperthermia. (18) In response to hyperthermia, normal tissue will show a dramatic and temperature dependent increase in blood flow at temperatures up to 50°C. In contrast, blood flow through neoplastic tissue will increase to a much smaller extent and stasis occurs at lower temperatures which are well tolerated by normal tissue. Therefore, there appears to be two fundamental mechanisms by which supranormal temperatures can be selectively toxic to neoplastic cells via both direct cytotoxic effects and vascular stasis.

As mentioned, for drugs administered into the peritoneal cavity, the simultaneous systemic administration of neutralizing agents can provide protection against the systemic toxic effects of drug which leaks into the circulation. Systemic sodium thiosulfate has been shown to covalently bind and inactivate cisplatin in the systemic circulation and obviate the expected renal toxicities. The use of sodium thiosulfate allows the administration of high doses of intraperitoneal cisplatin which might result in blood levels comparable to an intravenous administration of drug. (19) A loading dose of sodium thiosulfate, followed by continuous infusion has completely prevented any substantial rise in serum creatinine with doses of cisplatin up to 270 mg/M^2 administered intraperitoneally with a 4-hour dwell time.

The major disadvantage of intraperitoneal drug administration appears to be that drug uptake by tumor tissue is mostly through capillary diffusion rather than capillary flow. With cisplatin in a normothermic environment, tumor penetration up to 3 mm has been shown. This would theoretically be adequate to penetrate a tumor deposit 6 mm in diameter. Thus it is clear that aggressive surgical debulking, leaving minimal gross residual disease, will be optimal for the maximum therapeutic effect with cisplatin.

In adult studies of carcinomatosis, there were no procedure related mortalities; morbidity included renal impairment, ascites, and pancreatitis. Dose limiting toxicity included grade III leukopenia, grade IV neutropenia and grade III and IV thrombocytopenia at the higher doses only (greater than 800 mg/M^2). (20, 21) Specifically, no patient had a prolonged postoperative ileus and no adverse effect on wound healing was observed. Following surgery, the median time before tolerating enteral feeds was 5 days (range 1-7 days), and patients could tolerate a regular diet at a median of 7 days (range 4-8 days). Neither patient who had undergone bowel resection and anastamosis followed by HIPEC had any anastamotic complication. One patient suffered a subfascial hematoma incurred from trauma to the left inferior epigastric artery. (20) In the mesothelioma study, the MTD of cisplatin was 300 mg/M^2. Above this dose there were significant rises in creatinine and one patient required temporary hemodialysis. (21) There have not been any untoward effects of the HIPEC on the ability of these patients to heal incisional wounds and convalesce uneventfully.

This intraoperative treatment using HIPEC in children has provided some very encouraging results. The phase I study of HIPEC in children done here (protocol #2005-0917) proved to be safe. There were no protocol related deaths. Two SAE's included temporary cardiomyopathy likely related to the 4 kg+ tumor resected and supraventricular tachycardia likely related to central venous catheter malposition. Several children had temporary increased creatinine, up to 1.9. However, no problems were seen with urinary output; serum creatinine returned to normal within 1-2 weeks without treatment or dialysis.

Preliminary results suggest 3 year disease free survival is 71% (compared to 26% in historic controls) and disease free interval is increased 5 times from 1.6 to 9 months in the subset of patients with DSRCT. The 2 sarcoma patients died within 6 months and one mesothelioma patient is alive with minimal disease. Another mesothelioma patient in 3rd relapse was treated with surgery + HIPEC is >2 years from surgery. In summary there appears to be benefit in many and we have reached a dose limiting toxicity (DLT), elevated creatinine using HIPEC with cisplatin at 150 mg/M^2.

Rationale

Desmoplastic small round cell tumor (DSRCT) is a rare disease of children, adolescents and young adults, which begins in the abdominal cavity. Less than 200 cases are reported in the world literature. The primary organ of DSRCT origin is the peritoneum. It is a very unique tumor that is difficult to treat because of the infiltrative and diffuse nature of the peritoneum. Patients may present with dozens to hundreds of tumors studding the peritoneal cavity. DSRCT was only recently described in 1991 and since then multimodality treatment including chemotherapy, radiation and aggressive surgery, has not improved outcome. Here at UT MDACC the PI has conducted a phase I trial in children with 'carcinomatosis' who underwent continuous hyperthermic peritoneal perfusion using cisplatin after cytoreductive surgery. (This was an investigator initiated trial and we were the only center in the North America embarking on this effort)

For continuity, we propose to open the phase II study on the subset of patients with the best prognosis after HIPEC, those with DSRCT. In data not yet published, we compared the 9 patients with DSRCT who have undergone HIPEC with 15 historical adolescent and adult patients with DSRCT at UT MDACC who had chemotherapy +/- radiation therapy only and no HIPEC and found a survival advantage of 41 weeks in the patients undergoing HIPEC, a 3 year median survival of 26% for those not undergoing HIPEC and 71% for those who had HIPEC. This is very preliminary data with few patients and follow up is only 1-3 years. Further study of HIPEC in DSRCT is warranted. The surgical study plan and delivery of hyperthermic chemotherapy are the same as the previously approved phase I protocol. The maximum tolerated dose, the safe dose of cisplatin found in phase I, is 100 mg/M^2. Pediatric and adult patients with other non-carcinoma tumors with extensive peritoneal disease will be eligible if no standard HIPEC treatment has been established for these patients. Results of the research analysis will not be shared with the patient during the conduct of this study nor will the results influence the clinical strategy.

1.0 Primary objectives of the study

Primary objective 1: To determine the efficacy of HIPEC using hyperthermic cisplatin given as a continuous perfusion after complete abdominal tumor excision in patients with DSRCT.

Primary objective 2: To determine the morbidity of extensive tumor resection and HIPEC on patients with DSRCT and other non-carcinoma tumors with extensive abdominal disease.

Methods and Research Plan

The current study is designed to evaluate the efficacy of HIPEC with cisplatin, in children adolescents and young adults with disseminated intra-peritoneal disease. This phase II pilot study will include aggressive surgical debulking, in patients with abdominal desmoplastic small round cell tumor.

2.0 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 Inclusion Criteria

2.1.1 Age greater than or equal to 1 year.

2.1.2 Histologically or genetically proven diffuse peritoneal or retroperitoneal tumor from desmoplastic round cell tumor, ovarian germ cell, sarcoma, Wilms' tumor, or other non-carcinoma tumors.

2.1.3 Radiologic workup must demonstrate that the disease is confined to the abdominal cavity

2.1.4 Radiologic workup or prior abdominal exploration must be consistent with disease which can be debulked to a residual size of less than or equal to 1 cm thickness per tumor deposit

2.1.5 Patients must have a minimum expected duration of survival of greater than 6 weeks as determined and documented by the attending surgeon or medical oncologist.

2.1.6 Patients must not have any systemic illness which precludes them from being an operative candidate as determined by anesthesia preoperative evaluation. This includes but is not limited to, sepsis, liver failure, pregnant or lactating females.

2.1.7 Patients must have fully intact mental status and normal neurologic abilities. Intact mental status is defined by 'the capacity to identify and recall one's identity and place in time and space.' Assessment of mental status and documentation of fully intact mental status will be completed using physical and mental exam by the referring doctor or oncologist.

2.1.8 Patients must have adequate renal function (serum creatinine $\leq$ 1.5 mg/dl without history dialysis or renal failure or creatinine clearance less than 50 mL/min/1.73 M^2 if less than 5 years of age)

2.1.9 Patients will be eligible if the WBC is $\geq$2000/µl or ANC is $\geq$1,500 and platelets are $\geq$ 100,000/mm^3

2.1.10 Patients will be eligible if serum total bilirubin and liver enzymes are $\leq$ 2 times the upper limit of normal

2.1.11 Patients must be recovered from any toxicity from all prior chemotherapy, immunotherapy, or radiotherapy and be at least 14 days past the date of their last treatment

2.2 Exclusion criteria

2.2.1 Patients will be ineligible if they have any concomitant cardiopulmonary disease which would place them at unacceptable risk for a major surgical procedure

2.2.2 Patients will be ineligible if they have disease outside of the abdominal cavity which is uncontrolled

2.2.3 Patients will be ineligible if they have a baseline neurologic toxicity of Grade 3 or greater (because of the potential neurotoxicity associated with platinum)

2.2.4 Patients who have failed previous intraperitoneal platinum therapy will be ineligible ("Failed" is having disease recurrence $\leq$ 3 months.)

2.2.5 Patients with Retroperitoneal Liposarcoma will be ineligible

2.3 Research Eligibility Evaluation

2.3.1 A complete history and physical examination

2.3.2 Chest, abdomen and pelvic CT scan or MRI within 3 weeks of study entry

2.3.3 Blood tests including, CBC, PT/PTT, sodium, potassium, chloride, carbon dioxide, BUN, creatinine, calcium, amylase, magnesium, phosphorus, AST, ALT, total bilirubin, alkaline phosphatase, albumin within one week of study entry

2.3.4 Bone scan and brain MRI as clinically indicated within two weeks of study entry

2.3.5 Echocardiogram and ECG required within two weeks of study entry

2.3.6 Review of pathology slides of tumor specimen obtained from biopsy or surgical resection, by MDACC pathologist (unless genetic confirmation is previously obtained)

2.3.7 Urine pregnancy test will be required per institutional pregnancy assessment. (Policy no. CLN1114)

2.3.8 Audiology evaluation will be done before beginning therapy as a baseline

2.3.9 Patients under 5 years of age must have a 24 hour urine collection for creatinine clearance. The value obtained from the lab at MDACC will be multiplied by 1.73 and divided by the patients BSA to obtain the corrected creatinine clearance in the units mL/min/1.73 M^2

3.0 Study Implementation: Surgery

3.1 Procedures and therapeutic agents

3.1.1 Each operation will be carefully planned and informed consent obtained from the patient 18 or older or the parents (and assent from child if age appropriate) after a detailed discussion of possible complications, risks and possible benefits.

3.1.2 A general anesthetic is administered and the patient is placed on a cooling blanket that will initially not be turned on). Esophageal and bladder temperature probes will be inserted. Unless already in place upon arrival to the OR; a central venous catheter, large bore IV's and an arterial line will be placed. An exploratory laparotomy will be performed. If the surgeon determines the operation to be feasible and safe, a debulking operation will be performed which will include all disease possible, leaving tumor nodules no greater than 1 cm thick. If the surgeon determines that the patient cannot be cytoreduced leaving no tumor nodules in aggregate greater than 1 cm, patients will not receive HIPEC. These patients may then receive surgical debulking but will not be eligible to be enrolled on this protocol. The extent of the operation will vary depending on the tumor. Possible procedures include partial liver resection, partial, limited pancreatic resection, splenectomy, or bowel resection. Non-surgical ablation of liver tumors is acceptable.

3.1.3 HIPEC- After cytoreductive surgery and lysis of adhesions, two large bore catheters are placed in the peritoneal cavity through the incision. The first is placed over the dome of the liver for perfusion influx and a second catheter is placed so that the tip lies in the pelvis for perfusion efflux. Up to eight temperature probes are placed beneath the peritoneal surface or at the influx and efflux catheters. The abdominal incision is closed and HIPEC is performed.

3.1.4 HIPEC and Cisplatin- Thirty minutes before HIPEC is begun, body temperature is cooled to 35°C. During the procedure, the cooling blanket and ice packs at the patients head and legs will be adjusted as necessary to maintain core body temperature below 38.5°C (as measured by esophageal probe). The catheters are connected to a perfusion circuit. The perfusate passes from a reservoir through a roller pump, heat exchanger and then into the abdominal cavity. Efflux from a second catheter is then recirculated through the reservoir and pump. The perfusion flow rate will be maintained to distend the abdomen 5 (±2) liters/minute, and a perfusate volume will be maintained which moderately distends the abdominal cavity. Before the instillation of Cisplatin, the peritoneal cavity is warmed to a target of 40°C (±1°C) as estimated by the influx/efflux catheter or peritoneal probe and the anesthesiologist will hydrate the patient with isotonic solution. The perfusion is continued for 90 minutes after adding the cisplatin. Cisplatin at 100 mg/M^2 (1mg/1mL concentration in syringes) is to be added to the perfusate. The total maximum dose will not exceed

130 mg. Constant physical manipulation of the abdomen is maintained for the entire 90 minutes to assure even distribution of the perfusate. Peritoneal temperature is measured every 10-15 minutes by up to eight probes placed either beneath the peritoneal surface or at the influx and efflux catheters. At the end of the perfusion, the abdomen is re-opened and the perfusate is again irrigated from the abdominal cavity. The bowel is then thoroughly re-inspected for any perforations incurred and bowel anastamosis are completed. Throughout the procedure urine output must be maintained at 1-2 cc/kg/hr. Post-operative hydration will include 1.5 x maintenance normal saline or lactating ringer and maintenance of urine output of at least 1cc/kg/hr and replacing urine output cc/cc every hour with normal saline, for the first 48 hours to prevent hypovolemia and renal failure.

3.1.5 Retroperitoneal tumors- In the case of a retroperitoneal tumor, after tumor debulking, exposure of the entire retroperitoneum in the area of the tumor bed, will be maintained. The remainder of the procedure will be the same as above. Stable perfusion parameters are obtained and the peritoneal cavity is warmed to a minimum of 40°C (±1°C), prior to adding the cisplatin. The perfusion is continued for 90 minutes after adding the cisplatin. At the end of the perfusion the perfusate is irrigated from the abdominal cavity and the abdominal wall is closed in the usual fashion.

3.1.6 Sodium thiosulfate- In order to limit the systemic toxicity of cisplatin, sodium thiosulfate will be administered by loading dose and then a 12 hour continuous intravenous infusion. A loading dose of 7.5 gm/M^2 (maximum 12.5 gm) of sodium thiosulfate will be diluted in 20 ml/kg of 0.9% normal saline up to 500 mL. This loading dose will be infused over 20 minutes beginning 30 minutes (± 15 minutes) after the addition of cisplatin to the peritoneal perfusion circuit. Then maintenance infusion of sodium thiosulfate 1.275 gm/M^2/hr for 12 hours will be delivered by infusion pump

4.0 Data Collection and Evaluation

4.1 Data Collection

All patients will be entered in PDMS/CORe with fields to reflect the information on the data collection forms included in Appendix 1.

4.2 Response Criteria and Statistical Considerations

4.2.1 This is a phase II study of continuous hyperthermia peritoneal perfusion (HIPEC) in patients with desmoplastic round cell tumor (DSRCT) and non-DSRCT patients. The primary objective is to assess the efficacy of this treatment, with a primary endpoint of time to relapse. The historical median time to relapse for DSRCT patients without HIPEC treatment was about 1.6 months. A maximum of 22 patients will be enrolled in MDACC at an estimated accrual rate of 1 patient every 2 months including a total of 5 non-DSRCT patients. Patients will be followed up until relapse, death or for 6 months after the treatment, which ever occur first. It would be encouraging if the median time to relapse could increase to 3.2 months with the HIPEC treatment. The toxicity and efficacy will be monitored during the study, and all the data will be used to update the prior distributions for toxicity and efficacy parameters. The study will be stopped for toxicity and futility based on the following stopping rules.

4.2.2 The primary endpoint TTP will be monitored using the method of Thall et al. (23). Denote median (TTP) = m_H for patients without HIPEC treatment and m_E for patients with HIPEC treatment. We assume that TTP is distributed exponentially with mean of m_H and m_E, respectively, in patients without and with HIPEC treatment. Under a Bayesian model, we will further assume that m_H has an inverse gamma (IG) prior with parameters (16.2, 24.3), with a mean of median TTP=1.6 months and variance = 0.18. We also assume that m_E follows IG prior (2.03, 1.64) with the same median TTP as m_H but with a much larger variance (100) to reflect much greater uncertainty about TTP in patients with HIPEC treatment. The TTP data will be monitored continuously, and the study will be terminated early if $Pr(m_H + d < m_E \mid data) < 0.05$, where d= 1.6 month. Specifically, the trial will be stopped early if, given the current data, there is less than 5% chance that the median TTP will improve by more than 1.6 month in patients treated with HIPEC, compared to those without HIPEC treatment. The operating characteristics of this decision rule are summarized in Table 1.

4.2.3 In addition, toxicity will be monitored closely in all patients. The evaluation of the toxicity data will begin after enrollment of 8 patients. Denote the probability of toxicity by θE, where toxicity is defined as any Grade 3 or greater renal, cardiac, respiratory or Grade 4 hematologic complications attributable to HIPEC. We assume $\theta E \sim$ beta (0.6, 1.4). Our stopping rule is given by the following probability statement: $Pr(\theta E > 0.30 \mid data) > 0.8$. That is,

we will stop the trial if, at any time during the study, we determine that there is more than 80% chance that the toxicity rate is more than 30%. Stopping boundaries corresponding to this stopping rule are to terminate the trial if (# Grade 3 or greater renal, cardiac, respiratory or Grade 4 hematologic complications) / (# patients evaluated) ≥4/8, 5/9, 6/12, 7/15, 8/18. That is, the trial will be stopped if 4 or more patients out of 8 patients, 5 or more patients out of 9 patients, and 6 or more patients out of 10, 11 and 12 patients, 7 or more patients out of 13, 14 and 15 patients, 8 or more patients out of 16, 17, 18 patients experience toxicity. Please note that for the first 8 patients, if 4 or more out of 4-7 patients experience toxicity, the trial will also be stopped, because the stopping boundary is already passed. The operating characteristics are summarized in Table 2.

4.2.4 Analysis Plan: For discrete or categorical data, descriptive statistics will include tabulations of frequencies. For continuous data, summary statistics including n, mean, standard deviation, median, minimum and maximum will be computed. The median time to progression and its 95% confidence interval will be estimated. Kaplan-Meier method, Log rank test and Cox proportional hazards regression modeling will be utilized to analyze time to progression and overall survival. The study will use Department of Biostatistics Clinical Trial Conduct website to conduct/monitor with regard to the defined Bayesian rules.

Table 1. Operating characteristics for the design

True median Time to progression (month)	Pr(stop early)	Average Number of Patients Treated (25th, 75th percentiles)
1	0.998	4 (1,5)
1.6	0.775	9 (2,18)
3.2	0.178	17 (2,20)
4	0.126	18 (20,20)

Table 2.

True toxicity rate	Early Stopping Probability
0.1	0.006
0.2	0.094
0.3	0.344
0.4	0.665
0.5	0.897

4.3 Pathologic response criteria

4.3.1 At the completion of cytoreductive surgery, one 1cm nodule will remain in the peritoneal cavity during the perfusion procedure. [redacted] One nodule of tumor removed before hyperthermic perfusion treatment will be preserved for comparison. Tumor nodules will be divided in three portions and preserved in paraffin, a frozen block and as snap frozen tissue. Slides will then be cut and then used for immunohistochemical analysis of apoptosis, proliferation and autophagy.

4.3.2 Snap frozen tissue will be used for RNA extraction and gene expression profiling for the purpose of categorizing patient tumors based on response to hyperthermic peritoneal perfusion treatment. The Illumina platform will be used. A comparison of 6 patient samples, pre and post treatment, for a total of 12 samples will be analyzed. We will create a log of response comparing pre and post treatment gene expression and identify gene signatures for pathologic vs. non pathologic responders. Paraffin embedded samples will be used for tissue microarray, comparing pre and post treatment, to validate gene expression data at the protein level using IHC. Upon completion of full analysis, the tissue samples will be destroyed.

4.3.3 This information will be critical in the future in that it will allow the treating physician to identify which DSRCT patients would best respond to hyperthermic peritoneal perfusion cisplatin treatment by genetic tumor characteristics. (Dr. Alexander Lazar, pathologist, is part of the sarcoma center under the direction of Dr. Lev)

4.4 Re treatment criteria

4.4.1 If patients return with recurrent measurable disease and experienced a 6 month disease free interval since the last HIPEC, they will be offered a reperfusion when there is radiographic evidence of recurrent intra-abdominal disease and no new contraindications. Patients having a reperfusion will be treated with 50 mg/M^2 of cisplatin. (This is based on renal insufficiency seen in 2 patients who underwent 2 perfusions at 100 mg/M^2)

4.4.2 Patients who progress will be offered other treatment alternatives

4.5 On study evaluation

4.5.1 Patients will undergo laboratory tests, imaging and physical exam as per on study criteria.

4.5.2 During HIPEC patients will have continuous core temperature monitoring by the esophageal probe and bladder probe. Peritoneal temperature is measured every 10-15 minutes by up to eight probes placed either beneath the peritoneal surface or at the influx and efflux catheters. If the temperatures are increasing above 40°C (±1), the temperature of the perfusate will be reduced. If the temperature readings are too low, the emphasis of the manual agitation will be redirected to that area of the abdomen.

4.5.3 Patients will be followed postoperatively with daily CBC, sodium, potassium, chloride, carbon dioxide, BUN, creatinine, AST, ALT, calcium, albumin, magnesium, phosphorous, total bilirubin, alkaline phosphatase, amylase for 5 +/-2 days and then twice weekly until discharge; and post-discharge at day 14+/-3 days and day 30+/- 3 days and at 3 and 6 month (+/-2 weeks) follow-up (Appendix 1) Adverse events will be assessed on the same timetable.

4.5.4 Patients will be monitored in the PICU no less than 48 hours. If necessary, adult patients will be admitted to ICU.

4.5.5 Evaluation of measurable disease will be performed one month, 3 months and 6 months postoperatively (+/- 2 weeks) using CT or MRI and physical exam. (CT or MRI scan performed only at 3 and 6 months)

4.5.6 Audiology evaluation will also be performed at one month evaluation.

4.6 Concurrent Therapies

4.6.1 Patients will be allowed to proceed with any post-operative chemotherapy including allogeneic or autologous bone marrow transplantation. No concurrent medications will be given at the time of study drug administration since this is only a 90 minute period in the operating room. However, baseline medications and all medications through the 30 days follow up will be entered into PDMS/CORe.

4.7 Pharmacokinetics (Optional)

4.7.1 Blood and peritoneal fluid samples (2.0 ml) will be collected in purple top tubes, centrifuged, and supernatant or plasma collected and stored at -20°C until analyzed.

4.7.2 Blood and peritoneal fluid will be collected prior to the start of cisplatin-HIPEC and then at times 0, 30, 60 and 90

minutes. An additional blood sample will be collected 24 hours (+/- 8 hours) after the start of HIPEC.

4.7.3 Platinum levels in plasma and perfusate will be determined by the laboratory.

4.7.4 Pharmacokinetic profiles of cisplatin in plasma and perfusate will be determined and compared.

4.8 Off Study Criteria

4.8.1 Progression of disease- Once patients demonstrate progression of disease at follow up MRI or CT or PET-CT scans at 3 or 6 months, other therapies may be offered (but are not considered part of this study). Disease progression is defined by radiographically visible nodules greater than 1.5 cm. However, patients would be followed until death even after the 6 month follow-up by notification by primary oncologist.

4.8.2 Voluntary withdrawal

4.8.3 Non-compliance with follow-up scheme

4.8.4 At the time of cytoreductive surgery if patients are found to have disease which cannot be debulked to a diameter <1 cm in aggregate will be taken off study and not given the perfusion treatment.

4.9 Serious Adverse Event Reporting (SAE)

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

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IRB.**
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IRB, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events**, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the IRB.
- **The MDACC "Internal SAE Report Form for Prompt Reporting" will be used for reporting to the IRB.**
- **Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**
- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IRB. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IRB according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

The PI is responsible for ADR reporting. Adverse events will be documented according to the recommended adverse event recording guidelines for Phase II protocols as seen below.

Recommended Adverse Event Recording Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

5.0 Human Subjects Protection

5.1 Rationale for use in children- Presently there is no standard treatment in children for tumors limited to peritoneal or retroperitoneal metastasis. In combination with other intravenous agents cisplatin has shown activity against various refractory, solid, pediatric tumors. In the treatment of many recurrent solid tumors, cisplatin is utilized as part of the intravenous regimen. Its use in HIPEC in adults has been promising. The PI has experience with this procedure in children and is the only one who will be performing the HIPEC procedure.

5.2 Informed Consent Benefits, Risks, Discomforts and Alternatives

5.2.1 Consent and Assent -- The investigational nature and objectives of this trial, the procedures involved and the attendant risks, discomforts, potential benefits and potential alternative therapies will be carefully explained to the adult patient (>/=18 year old) or to the parent and when appropriate, the child, prior to treatment and prior to obtaining a signed informed consent as well as assent from the child. These discussions will take place in the clinic setting as well as the hospital. During the initial consultation, the parents are presented a forthright and detailed overview of the experimental nature of the procedure, its theoretical advantages and disadvantages

and an overview of the operative procedure and anticipated convalescence. The fact that the patient must 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 adult patient (>/=18 year old) and/or parents will be informed that this therapy could make the patient or the child extremely ill and the risks of experiencing short or long term adverse effects from this treatment are high. The adult patient (>/=18 year old) and/or family is asked to review the informed consent document, encouraged to make notes, and a follow up discussion is scheduled either by phone or in person with the physician or nurse investigator and any additional questions will be answered prior to considering treatment on this protocol. At the time of consent and again the day of surgery, the family is reassured that participation in the trial is entirely voluntary and that they can withdraw or decide against treatment at any time without adverse consequences. Signed consent will be verified by the surgeon responsible for the care of the patient. A child life advocate will be a part of the informed consent process when the patient is a child.

5.2.2 Risks and Benefits- The potential benefit to a patient undergoing this therapy would be palliation in terms of preventing or delaying intra-abdominal tumor progression, which can be a devastating and painful source of symptoms and cause for demise. In addition, significant tumor response may extend survival. The risks of this protocol include those inherent to extensive abdominal surgery. This includes postoperative bleeding, wound infection, intra-abdominal abscess, wound dehiscence, enterocutaneous fistula, anesthetic complications and postoperative death. Also, toxicities of cisplatin therapy place the patient at risk. In addition, in the case of intra-abdominal catastrophe, patients may require re-operation.

5.2.3 Alternatives - Children dying of extensive peritoneal, retroperitoneal disease, or carcinomatosis, suffer with recurrent bowel obstructions, nausea, vomiting, abdominal pain, inability to pass stool, poor appetite and in late stages refractory ascites. Because there is presently no other treatment alternatives offered in this clinical scenario, aggressive treatment as a means of palliation and survival benefit, are justified. There have been many phase I and II trials in adults in which long term remissions after HIPEC in patients who were otherwise terminal, have been realized. Patients will be informed of other experimental chemotherapy options available.

6.0 Pharmaceutical Information

6.1 Cisplatin (cisplatin)

6.1.1 General

Cisplatin will be purchased from the Pharmacy for the use in this trial. Commercial supply of FDA approved Cisplatin will be used. For drug information: Cisplatin Aqueous formulation 1mg/ml concentration (Various Vendors). Lot numbers will be tracked per drug accountability requirements. It will be purchased by an institutional grant for this protocol.

6.1.2 Stability and Storage

Cisplatin is stable at controlled room temperature 15° - 25°C protected from light and 7 days under fluorescent room light. Further dilution at 0.05 or 0.5 mg/mL with 0.9% sodium chlorine injection (NS), USP, yields a solution that is stable for at least 24 Hours at room temperature. Intact vials in reconstituted solution should be maintained at room temperature. Do not refrigerate and protect unopened container from light.

6.1.3 Preparation

The total dose of cisplatin will be injected into a bag of 0.9% sodium chloride for injection, USP, to make 500 mL of final volume (± 10%) prior to administration.

6.1.4 Administration

Cisplatin-100 mg/M^2 {up to 130 mg/M^2 maximum dose} (in 500 mL) will be added to a stable perfusion system.

6.1.5 Toxicities

Cisplatin produces renal tubular toxicity's associated with renal insufficiency and electrolyte, (i.e. magnesium, potassium, calcium, phosphate, carbon dioxide) wasting which may result in significant hypomagnesaemia and hypokalemia. Neurotoxicity manifests as both sensory and motor peripheral neuropathies. Cisplatin is also toxic to the 8th cranial nerve producing ototoxicity which consists of primarily deficits in high frequency auditory acuity, but may include vestibular abnormalities. Systemic administration of cisplatin at doses similar to those planned in this study is associated with significant nausea and thrombocytopenia. Transient moderate elevations of hepatic transaminases and acute systemic allergic reaction including anaphylaxis may also occur. The prior phase I study of HIPEC with heated cisplatin has not identified any regional intraperitoneal toxicity from cisplatin and the dose to be used is 100 mg/M^2. The heat may cause a prolonged gastroparesis.

6.2 Sodium Thiosulfate

6.2.1 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.

6.2.2 Stability and Storage

Manufacturer's expiration date is present on the commercial formulation.

6.2.3 Preparation

A loading dose of 7.5 gm/M^2 (maximum 12.5 gm) of sodium thiosulfate will be diluted in 20 mL/kg of 0.9% normal saline up to 500 mL. An additional dose of sodium thiosulfate 1.275 gm/M^2/hr for 12 hours will be diluted in 0.9% normal saline for maintenance infusion.

6.2.4 Administration

Sodium thiosulfate will be administered by a loading dose and then a 12 hour continuous intravenous infusion. A loading dose of 7.5 gm/M^2 (maximum 12.5 gm) of sodium thiosulfate will be diluted in 20 mL/kg of 0.9% normal saline up to 500 mL. This loading dose will be infused over 20 minutes beginning 30 minutes ($\pm$ 15 minutes) after the addition of cisplatin to the peritoneal perfusion circuit. Then maintenance infusion of sodium thiosulfate 1.275 gm/ M^2/hr for 12 hours will be delivered by infusion pump.

6.2.5 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 intravenous administration of sodium thiosulfate has produced hypokalemia presumably due to an osmotic diuretic effect.

Appendix 1
Clinical and Laboratory Follow up

	Eval. days	Baseline (Pre-op)	D1	D2	D3	D4	D5	D11	D14	D30	3mo	6mo
Labs/ Tests												
Hb		X	X	X	X	X	X	X	X	X	X	X
Hct		X	X	X	X	X	X	X	X	X	X	X
Plt		X	X	X	X	X	X	X	X	X	X	X
Na		X	X	X	X	X	X	X	X	X	X	X
K		X	X	X	X	X	X	X	X	X	X	X
Cl		X	X	X	X	X	X	X	X	X	X	X
CO_2		X	X	X	X	X	X	X	X	X	X	X
BUN		X	X	X	X	X	X	X	X	X	X	X
Cr		X	X	X	X	X	X	X	X	X	X	X
Mg++		X	X	X	X	X	X	X	X	X	X	X
Ca++		X	X	X	X	X	X	X	X	X	X	X
Alb		X	X	X	X	X	X	X	X	X	X	X
PO_4		X	X	X	X	X	X	X	X	X	X	X
AST		X	X	X	X	X	X	X	X	X	X	X
ALT		X	X	X	X	X	X	X	X	X	X	X
Alk Phos		X	X	X	X	X	X	X	X	X	X	X
PT/PTT		X										
TB		X	X	X	X	X	X	X	X	X	X	X
Amy		X	X	X	X	X	X	X	X	X	X	X
PE		X	X	X	X	X	X	X	X	X	X	X
ECG		X										
Echo		X										
CT scan		X*									X	X
MRI		X*									X	X
Audio		X								X		
AE		X	X	X	X	X	X	X	X	X	X	X
PK			X									
Preg.		X										
24-hr UCr		X**										

*Choose one or both as clinically indicated. May include PET-CT. TB=total bilirubin, Audio=audiology, AE adverse events evaluation, PK= pharmacokinetic cisplatin level at 24 hours, Preg.=pregnancy test (blood or urine), Alb=Albumin, D=post op day

**24 hour urine collection for creatinine clearance calculation for children <5 years old

Optional PK Testing					
	0 (pre-perfusion)	30 min	60 min	90 min	24-hr (post-op)
Blood	X	X	X	X	X
Peritoneal Fluid	X	X	X	X	X

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