A Pilot Trial of Radiation Therapy "Sandwiched" between Paclitaxel and Carboplatin in Patients with Uterine Carcinosarcoma

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SCHEMA

SCHEMA

Weeks 1-9
Paclitaxel 175mg/m^2/3 hour & Carboplatin (AUC=6.0)
Repeat q 21 days x 3 cycles

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Weeks 8-13
Pelvic and Para-Aortic Radiation 6MV Photon Beam Energy
1.8 Gy Dose/Fx
Total Dose 45Gy

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Weeks 14, 15, 16
High Dose Radiation (HDR) x3, or IMRT where appropriate
Nucleotron Microselection Afterloading Technique
5 Gy to 0.5cm Depth from the Vaginal Cylinder Surface
Total Dose 15 Gy

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Weeks 14-22
Paclitaxel 175mg/m^2/3 hour & Carboplatin (AUC=5.0)
Repeat q 21 days x 3 cycles

1.0 BACKGROUND

Uterine carcinosarcomas represent approximately 4% of primary uterine malignancies [1]. However, our rates in the Bronx are about double the national rate likely due to a number of factors including the referral patterns and the ethnic and racial diversity of the community we serve at Montefiore Medical Center. Carcinosarcoma is an aggressive uterine tumor with a poor prognosis and a recurrence rate of 53% [2]. Sites of failure include pelvic and extrapelvic with most patients developing extrapelvic disease [3]. Pelvic radiation decreases the risk of pelvic recurrence, but has not been shown to improve overall survival [4, 5] secondary to extrapelvic recurrences and the hematogenous route of metastasis [3]. Chemotherapy agents demonstrating response in recurrent carcinosarcoma include adriamycin, cisplatin, ifosfamide and paclitaxel [6-10]. Combination chemotherapy has been shown to provide an improvement in response rate but with increased toxicity. In one GOG study, the combination of ifosfamide and cisplatin was compared to ifosfamide alone in recurrent carcinosarcoma. There was a 54% response rate with the doublet versus 36% with single agent cisplatin, but no difference in overall survival and a significantly increased rate of grade 3-4 toxicity in the doublet arm [10]. The combination of paclitaxel with ifosfamide was also studied by the GOG and there was an improved overall survival, 14 months with the doublet versus 8 months with ifosfamide alone. The response rate in the combination group was 45% compared to 29% with ifosfamide alone [11]. Neurotoxicity was considerably worse with the doublet chemotherapy (8% versus 30%).

The combination of paclitaxel and carboplatin has recently been studied for recurrent uterine carcinosarcoma. A retrospective review of 6 patients (five with primary disease) with advanced or recurrent carcinosarcoma, with no prior adjuvant treatment, that were treated with paclitaxel and carboplatin showed a response rate of 80%, a median progression free interval of 18 months and a median overall survival of 25 months [12]. This was one of the first studies that documented efficacy in an adjuvant setting with paclitaxel and carboplatin in carcinosarcoma. In a separate study, similar response rates were noted in a prospective phase II trial evaluating carboplatin and paclitaxel in advanced or recurrent carcinosarcoma. Patients that were treated with this regimen in the adjuvant setting had a median progression free interval of 15.8 months and median overall survival of 20.2 months. The overall response rate was 64% [13]. Another study showed similar response rates (60% in newly diagnosed patients and 55% in recurrent disease) of carboplatin and paclitaxel in carcinosarcoma when compared to the combination of ifosfamide and paclitaxel but with better tolerability and more convenience due to outpatient administration, unlike ifosfamide which requires the addition of Mesna and often inpatient administration [14]. This study also included patients that had prior radiation therapy. In GOG 232, the combination of paclitaxel and carboplatin was given to patients with advanced stage or recurrent carcinosarcoma who had not had previous chemotherapy and had measurable disease. 46 patients were eligible, 65% had primary disease, 35% had recurrent disease, and 33% had prior radiation therapy. 59% of patients completed 6 or more cycles. The overall response rate was 54% which is comparable to the other studies using carboplatin and paclitaxel in uterine carcinosarcoma. The median progression free survival was 7.6 months and overall survival was 14.7 months which is comparable to ifosfamide and paclitaxel. The toxicity profile was more favorable

with the carboplatin and paclitaxel combination [15].

Use of radiotherapy alone does not control extrapelvic recurrences. In one study, patients with stage I or II carcinosarcoma were treated with surgery versus surgery followed by radiotherapy. There was a trend towards fewer pelvic recurrences in the patients who received whole pelvic radiotherapy compared to those who did not ($p=0.09$) [4]. Other studies showed a statistically significant lower rate of pelvic recurrence in patients who received radiotherapy compared to those who did not, 28% versus 48% ($p=0.0002$) [16] and 3% versus 55% ($p<0.0001$) [17]. In a separate study evaluating the impact of multi-modal therapy on survival in patients with uterine carcinosarcoma, there was noted a longer median disease specific survival ($p<0.001$) and disease free survival ($p=0.02$) in patients that received a combination of chemotherapy and radiotherapy [18].

Multiple studies have demonstrated a response of carcinosarcoma to carboplatin and paclitaxel as well as the role of adjuvant radiotherapy in improvement in local control. We have had considerable experience here at Montefiore combining sequenced radiation therapy sandwiched with chemotherapy before and after radiation therapy for both carcinosarcoma and uterine papillary serous carcinoma [19, 20]. In our most recent carcinosarcoma trial, 27 patients with surgical stage 1-4 uterine carcinosarcoma, without evidence of gross disease, were treated with adjuvant ifosfamide/cisplatin or ifosfamide for three cycles, then received pelvic external beam radiotherapy and brachytherapy followed by three more cycles of ifosfamide/cisplatin or ifosfamide. The two year disease free survival for stage I patients was 18.75 months and for stages II-IV was 15.81 months [20]. Similar to a GOG trial in the recurrent setting, in our adjuvant trial, toxicity was increased in patients who received ifosfamide with cisplatin without added efficacy [10]. Thus, in the last cohort of this trial, we dropped the cisplatin from the regimen because it was adding toxicity without benefit. In our uterine papillary serous carcinoma "sandwich" trial, 30 patients with surgical stages I-IV, without evidence of gross residual disease received adjuvant paclitaxel/platinum for three cycles, followed by external beam pelvic radiotherapy and brachytherapy, and then three more cycles of paclitaxel/platinum. The three year disease free survival for stage I/II patients was 69% and for stage III/IV patients was 54%. 29 out of the 30 patients completed the protocol with grade 3/4 neutropenia occurring in 42% of cycles. 6 out of 177 cycles were delayed 1 week for neutropenia [19]. Both in-house trials of sequenced chemotherapy and radiation therapy resulted in higher than expected survival in the adjuvant setting. Due to the recent reports of efficacy of paclitaxel and carboplatin in recurrent carcinosarcoma, this pilot protocol is designed to determine the toxicity and clinical benefit of radiation therapy "sandwiched" between three cycles of paclitaxel and carboplatin before and after radiation therapy.

2.0 OBJECTIVES

2.1 To assess the one year recurrence-free survival in patients with uterine carcinosarcoma treated with "sandwich" therapy-including defining the patterns of recurrence in patients with carcinosarcoma who were treated with this regimen.

2.2 To evaluate the toxicity and tolerability of pelvic radiation "sandwiched" between cycles of paclitaxel/carboplatin chemotherapy in patients with uterine carcinosarcoma: [paclitaxel/carboplatin (x 3 cycles)* radiation therapy* paclitaxel/ carboplatin (x 3 cycles)].

2.3 To correlate surrogate endpoint biomarkers with progression-free survival and prognosis.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

Patients may be included in the study if all of the following criteria are met:

a. Histologically documented uterine carcinosarcoma with no visible residual disease.
b. Surgical staging to include total abdominal hysterectomy, bilateral salpingo- oophorectomy, peritoneal washings, and lymph node samplings.
c. Patients must be entered no more than 12 weeks post operatively
d. Age $\geq$ 18 years.
e. ECOG performance status of < 2.
f. Written voluntary informed consent.

3.2 Exclusion Criteria

Exclusion from the study will be required if:

1. Patient has impairment of hepatic, renal or hematologic function as defined by the following baseline laboratory values:

   a. Serum SGOT and /or SGPT > 2.5 times the institutional upper limit of normal
   b. Total serum bilirubin > 1.5 mg/dl
   c. History of chronic or active hepatitis
   d. Serum creatinine > 2.0 mg/dl
   e. Platelets < 100,000/mm3
   f. Absolute neutrophil count (ANC) < 1500/mm3
   g. Hemoglobin < 8.0 g/dl (the patient may be transfused prior to study entry)

2. Patient has severe or uncontrolled concurrent medical disease (eg. uncontrolled diabetes, unstable angina, myocardial infarction within 6 months, congestive heart failure, etc.)

3. Patient with any prior chemotherapy or radiotherapy for pelvic malignancy.

4. Patients with any history of cancer with the exception of non-melanoma skin cancer are excluded if there is any evidence of other malignancy being present within the past five years.
5. Patients with dementia or altered mental status that would prohibit the giving and understanding of informed consent at the time of study entry.

4.0 REGISTRATION PROCEDURES

All patients must be registered by calling Loraine Centrilla RN at (718) 405-8082 and faxing registration forms to (718) 829-2408. Any questions regarding eligibility may be addressed with the P.I. or research coordinator.

5.0 TREATMENT PLAN

5.1 Dosing Guidelines

5.1.1 Chemotherapy

Paclitaxel is available commercially. Paclitaxel 175 mg/m2 will be given over 3 hours in 250-500 ml of 5% dextrose or normal saline. Premedication for prevention of anaphylactoid reactions with anti-histamines and/or steroids should be administered as per standard practice.

Carboplatin is available commercially. Carboplatin at an AUC of 6.0 prior to radiation and AUC of 5.0 following radiation is to be administered following paclitaxel in approximately 250 ml of normal saline over 30 minutes. AUC based dosing as described by Calvert et al. will be according to the following formula: Dose (mg) = AUC x (GFR + 25); the GFR is not to exceed 125ml/min. The initial GOG trial using combination paclitaxel and carboplatin therapy was performed on patients with optimally debulked ovarian epithelial carcinoma [21]. At that time, the carboplatin dose was an AUC of 7.5. Since then, multiple large cooperative trials have been performed using AUCs of 5.0. Despite the lower dosage of carboplatin, it did not appear to compromise the efficacy of the drugs with improved toxicity profile [22-24].

Where AUC is as stated above and GFR is the calculated renal function according to the method of Cockroft and Gault:

Creatinine Clearance (mL/min) = [140-Age (years)] x Weight (kg) x 0.85
72 x serum creatinine (mg/dl), where weight is actual weight in kg.

The normal range of serum creatinine is from 0.5 to 1.5 mg/dl. In patients of the same age with “normal creatinine”, their carboplatin dosage may vary significantly if one has a value of 0.5 and the other has a value of 1.0. Patients of the same age with a creatinine of 0.5 would have an astronomically higher dosage of carboplatin (two times) than the patient with a creatinine of 1.0. Therefore, we opt to arbitrarily use a creatinine of 0.7 mg/dl in the GFR calculation for all patients whose creatinine is at or below 0.7 mg/dl. While this may be arbitrary, it minimizes the potential significant toxicity associated with a very high carboplatin dosage, yet maintain doages for all patients at what we believe to be therapeutic values. In patients with abnormally low

serum creatinine (less than or equal to 0.7mg/dl), the creatinine clearance should be estimated using a minimum of 0.7mg/dl.

If a more appropriate (higher) baseline creatinine value is available from pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.

The maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min

The maximum allowed doses of carboplatin are:

AUC	Maximum Dose (mg)
6	900mg
5.5	825mg
5	750mg
4.5	675mg
4	600mg

Chemotherapy will be administered every 21 days for 3 cycles. This will be followed by a 5-week chemotherapy break, while external beam radiotherapy is underway. The 4th cycle of chemotherapy will overlap with the High Dose Radiation (HDR). The remainder of the planned 6 cycles of paclitaxel/carboplatin therapy will continue to be administered every 21 days.

5.1.2 Radiation

Radiation therapy will be delivered after the 3rd cycle of chemotherapy. The total dose of external beam pelvic radiation is 45 Gy over 5 weeks. Patients will be treated once a day, 5 days a week, with a daily fraction size of 1.8 Gy. Four-field technique (AP-PA opposed and lateral opposed fields) will be used with a megavoltage beam of > 6MV and a minimum source-axis distance of 100cm. The fields may be extended in the case of ≥ 2 positive pelvic nodes or documented para-aortic lymph node disease.

All fields treated require simulation and custom designed blocks, as well as portal verification on the treatment unit. Small bowel series should be encouraged to exclude small bowel from the field. Pretreatment CT scan of the abdomen and pelvis will be used for planning para-aortic fields if needed. Sites of known positive nodes should be marked at the time of surgery with identifiable hemoclips.

Fields should be calculated by optimizing the dose distribution by obtaining isodose curves of the pelvis. All fields should be treated daily throughout the treatment course. The specification of target dose is in terms of a dose to a point at or near the center of the target volume. For the following portal arrangements, the target dose will be specified. For a 4-field arrangement of beams: at the isocenter of the beams, the maximum dose in the target volume should not exceed the central dose by more than 10%. Doses to critical structures must be recorded.

Pelvic Portal (AP-PA fields): Includes a superior border between L5 and S1; a lateral border 1-1.5 cm lateral to the widest true pelvic diameter; and an inferior border below the obturator foramen and at least 4 cm beyond the vaginal cuff. A radio-opaque marker in the vagina to mark the vaginal cuff will help to facilitate proper placement of the lower border.

Pelvic Portal (lateral fields): Includes a superior border identical to the AP-PA fields; an anterior border through the symphysis pubis and at least 1 cm anterior to common iliac nodes at L5-S1; a posterior border to include at least S1-S2; and an inferior border identical to AP-PA fields.

Para-aortic Portal: Includes a superior border of L1-L2 or 3 cm superior to the positive node site; an anterior border 3 cm anterior to the vertebral body; lateral borders 3 cm lateral to the vertebral body; and a posterior border that will exclude the spinal canal.

HDR brachytherapy, or Intensity Modulated Radiation Therapy (IMRT) where appropriate, involves a proximal 2/3 vaginal boost using the nucleotron microselectron remote afterloading technique. Three fractions of 5 Gy each will be prescribed to 0.5cm depth from the vaginal cylinder surface. Three doses of HDR or IMRT will be completed with in three weeks of completion of external beam radiation. The vaginal surface dose may be calculated at the vaginal surface lateral to the midpoint of the surface of the cylinder.

For HDR and IMRT, a report on the dose to bladder and rectum is mandatory. The bladder dose may be calculated at a reference point, which is obtained as follows: A Foley catheter balloon must be filled with 7 cm3 of radio-opaque fluid. On the lateral radiograph, the reference point is obtained on an anterior-posterior line drawn through the center of the balloon. The reference point is taken on this line at the posterior surface of the balloon. On the frontal radiograph, the reference point is taken at the center of the balloon. The rectal dose at several points may be calculated by using a flexible radio-opaque rectal marker.

5.2 Prevention of Anticipated Toxicity

The major toxicities to be expected from the combined modalities of treatment are hematologic and gastrointestinal. Complete blood counts will be monitored weekly for evidence of toxicity. Antiemetics and hydration will be administered to prevent nausea and vomiting.

Toxicities particular to paclitaxel include hypersensitivity reactions. Premedications (diphenhydramine, steroids, and H2 blockers) appear to reduce the incidence and severity of hypersensitivity reactions, but do not provide complete protection. Emergency agents (diphenhydramine, steroids and epinephrine) will be available. IV sites should be evaluated regularly for signs of infiltration as the Cremophor vehicle may cause tissue damage. In-line filtration with a 0.2-micron filter should be used.

Toxicities particular to carboplatin include nephrotoxicity, ototoxicity, peripheral neuropathy, electrolyte imbalance, hypocalcemia, hypomagnesemia, amino-glycoside

ototoxicity, ocular toxicity, and allergic reaction. Severe renal toxicity can be prevented by intravenous hydration and administration of mannitol.

Monitoring of electrolytes and inclusion of potassium and magnesium in intravenous hydration may prevent electrolyte abnormalities. Severe hypomagnesemia and hypocalcemia may require aggressive replacement therapy. Aminoglycoside antibiotics may potentiate renal toxicity and should be avoided if possible.

Ototoxicity and neurotoxicity are related to cumulative dose. Severe toxicity can be avoided by careful monitoring of symptoms. Patients should be queried about hearing loss and paresthesias prior to each course of carboplatin.
Expected radiation toxicities are fatigue, diarrhea, nausea, vomiting, rectal irritation, urinary frequency and dysuria, loss of pubic hair, reddening and irritation of skin in the irradiated field, and depression of blood counts. Long-term side effects may include chronic malabsorption, rectal ulcer, bleeding or stricture, dysuria, hematuria, bowel obstruction, dryness and shortening of the vagina, dyspareunia, vaginal vault necrosis and fistula formation between pelvic tissues.

5.3 Dose Reduction

Dose-limiting neutropenia is defined by the occurrence of febrile neutropenia or prolonged Grade 4 neutropenia persisting ≥7 days. Febrile neutropenia is defined within the NCI CTC v4.0 as an ANC <1000uL with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than one hour.

Dose level before RT	Carboplatin	Paclitaxel
0	AUC 6.0	175 mg/m^2
-1	AUC 5.5	175 mg/m^2
-2	AUC 5.0	175 mg/m^2
-3	AUC 5.0	Dose reduce by 20%

Dose level after RT	Carboplatin	Paclitaxel
0	AUC 5.0	175 mg/m^2
-1	AUC 4.5	175 mg/m^2
-2	AUC 4.0	175 mg/m^2
-3	AUC 4.0	Dose reduce by 20%

Dosing-limiting thrombocytopenia is defined by any occurrence of Grade 4 thrombocytopenia (25,000/uL) or bleeding associated with Grade 3 thrombocytopenia (25,000-<50,000/uL).

Dose level before RT	Carboplatin	Paclitaxel
0	AUC 6.0	175 mg/m^2
-1	AUC 5.5	175 mg/m^2
-2	AUC 5.0	175 mg/m^2
-3	AUC 5.0	Dose reduce by 20%

Dose level after RT	Carboplatin	Paclitaxel
0	AUC 5.0	175 mg/m^2
-1	AUC 4.5	175 mg/m^2
-2	AUC 4.0	175 mg/m^2
-3	AUC 4.0	Dose reduce by 20%

If the above occurs on day 21, therapy should be withheld (for a maximum of 21 days) until counts return to an ANC > 1500/uL and platelet count > 100,000/uL. Patients who received G-CSF prior to the current cycle may begin (day 1 of cycle) with ANC ≥ 1000 cells/uL, to allow for transient reductions in ANC after discontinuation of G-CSF. Patients who are delayed more than 7 days due to neutropenia may begin with ANC ≥ 1000 cells/uL if clinically appropriate; as they will receive G-CSF with subsequent therapy. Patients who have been delayed for more than 7 days due to neutropenia should receive G-CSF with subsequent cycles prior to dose reduction. G-CSF should be considered in all patients that have experienced grade 4 neutropenia.

All patients that exhibit chemotherapy related grade 3 and non-hematologic (eg mucositis and neuropathy) toxicities will follow the same dose reductions as for grade 4 hematologic toxicities displayed in the above tables.

Dose reduction for delayed hematologic (neutropenia and/or thrombocytopenia) recovery is as follow:

Delay (days)	Modification
1-7	No change
8-14	Reduce carboplatin by one AUC
14-21	Reduce paclitaxel by 20%
>21	Discontinue protocol

Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia.

If there is an interruption of more than one week, during radiation therapy, it should be completed to the prescribed total dose. If there are interruptions of more than two weeks, this will be considered a major deviation from the protocol, and resumption of therapy will be at the discretion of the principal investigator.

5.4 Adverse Event Reporting

An adverse event refers to any adverse medical change from the patient's baseline (or pretreatment) condition which occurs during the course of a clinical study, after starting treatment, whether considered treatment related or not.

Adverse events may be volunteered spontaneously by the patient, or be discovered as a result of general questioning by the investigator or by physical examination. Also to be reported is any patient requiring hospitalization while on protocol or any grade 4 hematologic or grade 3 or 4 non-hematologic toxicity.

All adverse events occurring during this clinical study must be reported to the principal investigator and accurately recorded in the adverse events form within 10 days of the toxic event.

Both chemotherapy and radiation treatment breaks should be noted and the reasons should be documented.

6.0 MEASUREMENT OF EFFECT

6.1 Recurrence-Free Survival

Recurrence-free survival is defined as date of entry to date of reappearance of disease. Site(s) and date of relapse will be recorded. Recurrent disease will be defined as pelvic or distant. Pelvic sites will be specified as vaginal or other, and distant sites will be specified as to their anatomic location. Relapse should be confirmed by histologic or cytologic evaluation when possible.

6.2 Toxicity

Toxicities will be graded according to the NCI Common Toxicity Criteria (version 4). Myelosuppressive toxicity shall be reported as the lowest observed white blood and platelet counts. Anemia and red blood cell transfusions will be noted.

Gastrointestinal toxicities shall be reported and hospitalizations for nausea, vomiting and diarrhea will be documented.

Patients will be followed for potential long-term toxicities with complete histories and physical examinations.

Any patient who receives at least one course of therapy and has follow-up information will be included for observation of toxicity.

7.0 STUDY PARAMETERS

7.1 Pre Study Evaluation

This evaluation requires completion within 14 days of registration, unless otherwise described. Baseline requirements will consist of a thorough history and physical

examination, including pelvic and rectovaginal exam. Evaluation of hearing loss and neuropathy is required. An ECG < 4 months prior to registration and laboratory tests will be obtained. Tests include, CBC with differential, platelet count, serum chemistry, including electrolytes, creatinine, BUN, glucose, magnesium, calcium, albumin, phosphorous, liver function tests, and urinalysis.

Histologic documentation of uterine carcinosarcoma is required. Prestudy CA125, CA19-9, CT scan of chest, abdomen and pelvis (within 28 days of therapy), and CXR (not required if CT of the chest) will be obtained.

7.2 Tests During Treatment

Day 13-15: CBC with differential and platelet count

Every 3 weeks: CBC with differential and platelet count electrolytes, BUN, creatinine, glucose, magnesium, calcium, phosphorous, albumin, CA125 and CA19-9.

After each Cycle: Complete review of systems and complete physical examination, including pelvic examination, clinical evaluation for ototoxicity and neuropathy. Weight and performance status will be documented.

7.3 End of Study Evaluation

This evaluation includes a complete history and physical examination and documentation of weight and performance status. Laboratory tests include a complete blood count with differential and platelet count, electrolytes, BUN, creatinine, glucose, magnesium, calcium, phosphorous, albumin, CA125 and CA19-9, urinalysis.

CT scan of chest, abdomen and pelvis will be obtained at the completion of the entire "sandwich" protocol or earlier if indicated.

7.4 Follow-up

Patients will be evaluated every 3 months for the first 2 years and every 6 months for the next 3 years. Evaluations at each visit include a complete history and physical examination and documentation of weight and performance status. Laboratory tests include a complete blood count with differential and platelet count, electrolytes, BUN, creatinine, glucose, magnesium, calcium, phosphorous, albumin, CA125 and CA19-9, urinalysis. CT Scans will be performed annually or earlier if indicated. After a total of 5 years, patients will be seen annually.

7.5 Secondary Endpoints

Staining of the pathologic specimens for ER/PR, HER2/neu and p53 will be performed by immunohistochemisty to assess for correlations with progression-free survival and prognosis.

7.6 Discontinuation

Criteria for stopping treatment include recurrence of disease; the development of unacceptable toxicity; and/or patient request.

8.0 DRUG FORMULATION AND PROCUREMENT

8.1 Drug Information:

Paclitaxel

Other Names: Taxol, NSC 673089

Classification: Antimicrotubule Agent

Mechanism of Action: Promotes microtubule assembly and stabilizes tubulin polymers by preventing their depolarization, resulting in the formation of extremely stable and nonfunctional microtubules, and consequently inhibition of many cell functions.

Storage and Stability: Vials are stored at room temperature. Freezing does not adversely affect the product. Solutions diluted to a concentration of 0.3 to 1.2 mg/ml in normal saline or 5% dextrose are stable for up to 27 hours when stored at room temperature and normal room light. Analyses of solutions filtered through IVEX-2 and IVEX-HP (Abbott) 0.2-micron filters showed no appreciable loss of potency.

Route of Administration: Intravenous
The concentrated solution must be diluted prior to use in normal saline, 5% dextrose and normal saline, or 5% dextrose in Ringer's solution to a concentration of 0.3 to 1.2 mg/ml. In-line filtration with a 0.22-micron filter should be used. Solutions exhibit a slight haze, common to all products containing nonionic surfactants. Glass, polypropylene, or polyolefin containers and non-PVC containing (nitroglycerin) infusion sets should be used. NOTE: Avoid the use of PVC bags and infusion sets, due to leaching of DEHP (Plasticizer). Solutions exhibiting excessive particulate formation should not be used.

Dose Specifics: Paclitaxel is given at a dose of 175 mg/m2 infused over three hours and repeated every 21 days. In minimally pretreated patients, doses up to 200-250 mg/m2 have been used.

Drug Interactions: Prior administration of cisplatin may increase myelosuppression because of reduced clearance of taxol. Ketoconazole may inhibit taxol metabolism, based on in vitro data.

Adverse Effects Profile: Neutropenia, thrombocytopenia, anemia, alopecia, injection sites reactions, radiation recall, rash, nausea, vomiting, mucositis, typhlitis, increased liver enzymes, hepatic failure and necrosis, sensory changes, peripheral neuropathy, arthralgia and myalgia, seizures, mood alterations, encephalopathy, motor and autonomic neuropathy, hypersensitivity (thought to be caused by Cremophor vehicle), atrial arrhythmia, sinus tachycardia and premature beats, syncope, hypotension, myocardial infarction, hypertension. Other: fatigue, headaches, light-headedness, myopathy, elevated serum creatinine, elevated serum triglycerides, and visual abnormalities.

Supplier: Commercially available.

Carboplatin

Other Names: CBDCA, Paraplatin ®, JM-8, NSC-241240

Classification: Second generation tetravalent organic platinum compound.

Mechanism of Action: Like cisplatin, carboplatin produces predominantly interstrand DNA crosslinks rather than DNA-protein crosslinks. Cell-cycle nonspecific.

Storage and Stability: Intact vials are stored at room temperature protected from light. The reconstituted solution is stable for at least 24 hours. When further diluted in glass or polyvinyl plastic to a concentration of 500ucg/ml, solutions have the following stability: in normal saline, 8 hours at 25 C, 24 hours at 5 C; in 5% dextrose (when reconstituted in sterile water), 24 hours at 25 or 5 C.

Route of Administration: Intravenous

NOTE: Avoid the use of aluminum, as carboplatin forms a precipitate.

Dose Specifics: The dose of carboplatin based on target AUC is calculated by the Calvert formula:

Dose (mg) = AUC x (GFR + 25).

Where AUC is 6.0 pre-radiation and 5.0 post-radiation and GFR is the calculated renal function according to the method of Cockroft and Gault:

GFR (ml/min) = 0.85 x {(140-age)/Scr)} x {wt(kg)/72}.

Where Scr is the serum creatinine level.
In patients with abnormally low serum creatinine (less than 0.7mg/dL), the creatinine clearance should be estimated using a minimum of 0.7mg/dl or cap the estimated GFR at 125mL/min based on the NCI guidelines.

Drug Interactions: Aminoglycosides may potentiate renal toxicity. Forms a precipitate when in contact with aluminum.

Adverse Effects Profile: Neutropenia, thrombocytopenia, anemia, rash, rare alopecia, hypersensitivity reactions, nausea, vomiting, increased liver enzymes, nephrotoxicity, elevations in serum creatinine and BUN, electrolyte losses (Mg, K, Na, Ca), peripheral neuropathy, rare ototoxicity, hypotension, flushing, chest pain, pruritis, bronchospasm, Other: pain, asthenia, flu-like syndrome.

Supplier: Commercially available.

9.0 STATISTICAL CONSIDERATIONS

To assess the one year recurrence-free survival in patients with uterine carcinosarcoma treated with "sandwich" therapy-including defining the patterns of recurrence in patients with carcinosarcoma who were treated with this regimen.. A total of 18 patients will be accrued to this study. One-year recurrence-free survival probability will be estimated, with 95% confidence limits based on exact methods for the binomial distribution. Conservatively, the sample size indicated will provide a 95% confidence interval with width of +/- 0.23. Frequencies will also be provided for side effects and adverse events.

Based on past accrual rates in this patient population, it is expected that accrual will be at most 4-6 per year for a total accrual period of about 48 months. Follow up will be a minimum of one year after the last patient is accrued in order to assess response. Therefore, total study time is expected to be 3.4-4.0 years.

10.0 COLLECTION PROCEDURES

Paraffin embedded tissue from uterine carcinosarcoma tumors will be stained for ER/PR, p53 and Her2Neu by immunohistochemistry.

11.0 RECORDS TO BE KEPT

Forms	To Be Submitted
Pathology Report	Within one week of registration
ECOG CTC Flow Sheet (#466R)	Baseline within one week of registration. On Treatment: Every month Off Treatment: See Follow-up

12.0 PATIENT CONSENT AND PEER JUDGEMENT

All institutional, state, and national guidelines concerning informed consent and peer review will be observed.

13.0 MINORITIES AND WOMEN STATEMENT

This study will be initially open to patients undergoing treatment at Montefiore Medical Center.

Although distributions may vary by disease type, our recruitment procedures have been developed to enroll patients who are representative of the target population.

14.0 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional, NCI and Federal regulations concerning the Informed Consent form will be fulfilled.

Annual reports will be provided to the Montefiore IRB.

15.0 ELIGIBILITY CHECKLIST

	Yes	**No**
Histologically documented uterine carcinosarcoma with no visible residual disease		
Surgical staging to include total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings, and lymph node sampling.		
Age ≥ 18 years		
ECOG performance status of < 2		
Written voluntary informed consent.		
Patient has no impairment of renal, hepatic or hematologic function as defined in section 3.2		
Patient does not have severe or uncontrolled concurrent medical disease (eg. Uncontrolled diabetes, unstable angina, myocardial infarction within 6 months, congestive heart failure, etc.)		
Patient has not had any prior chemotherapy or radiotherapy for pelvic malignancy.		
Patients has no dementia or altered mental status that would prohibit the giving and understanding of informed consent at the time of study entry.		

Patient Name_____

Patient MR#_____

Treating Physician_____

Principal Investigator_____
(Signature)

16.0 REFERENCES

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APPENDIX 1: STUDY SCHEDULE

Parameter	Pre-treatment	Day 13-15 (Cycles 1-6)	Each Cycle	Completion of Study	Follow-up Visit
History & Physical Exam	X		X	X	X
Pelvic Exam	X			X	
Weight, Performance, Status	X		X	X	X
CBC with differential, platelets	X	X	X	X	X
Electrolytes, Mg, BUN, Cr	X		X	X	X
SGOT, Bili	X		X	X	X
Urinalysis	X			X	X
CA-125, CA19-9	X		X	X	X
EKG	X[3]				
CXR	X				X[1]
CT chest/abd/pelvis	X[4]			X	X[2,1]
p53	X				
ER/PR	X				
HER2neu	X				

1. If clinically indicated.
2. Annually
3. With in 4 months of therapy
4. With in 28 days of therapy