IRB NUMBER: 08-03-060
IRB APPROVAL DATE: 03/22/2019

A Pilot Phase II Trial of Radiation Therapy "Sandwiched" between Paclitaxel and Carboplatin in Patients with High-Risk Endometrial Cancer After Standard Surgical Staging

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SCHEMA

SCHEMA

Weeks 1-9
Paclitaxel 175 mg/m^2/3 hours & Carboplatin (AUC=6.0)
Repeat q 21 days x 3 cycles
Weeks 13-21
Paclitaxel 175 mg/m^2/3 hours & Carboplatin (AUC=5)
Repeat q 21 days x 3 cycles

Week 8-13 Stage IAG3 with myometrial invasion plus LVI and IBG2 High Dose Rate (HDR) Brachytherapy x 5 Nucletron Microseleciton afterloading technique 5 Gy to 0.5cm Depth from the Vaginal Cylinder Surface Total Dose 25 Gy	Week 8-12 All other eligible patients Pelvic and paraaortic radiation 6MV Photon Beam energy 1.8 Gy Dose/Fraction Total dose 45 Gy
	Week 13, 14, 15 Hgh Dose Rate (HDR) Brachytherapy x 3 Nucleotron Microselectron Afterloading Technique 5 Gy to 0.5cm Depth from the Vaginal Cylinder Surface Total Dose 15 Gy

Weeks 13-21
Paclitaxel 175 mg/m^2/3 hours & Carboplatin (AUC=5)
Repeat q 21 days x 3 cycles

1.0 BACKGROUND

Uterine corpus cancer is a common gynecologic malignancy with an estimated 39,000 new cases in 2007.[1] It is also treatable if diagnosed at an early stage. However, patients with high-risk endometrial carcinoma have a significant risk of recurrent disease and mortality.[2,3,22] Surgical staging and debulking is standard for extirpation of gross disease, and adjuvant radiation therapy is recommended to treat patients who are at high risk for recurrent disease.[3-17] High-risk features include histologic cell type (endometrioid, clear-cell, and uterine papillary serous), grade, depth of myometrial invasion, cervical extension, lymph-vascular invasion, adnexal involvement, intraperitoneal spread, positive peritoneal cytology, and positive lymph nodes.[3,18]

Pelvic radiation can limit local recurrences to less than 6.5 percent. However, approximately 16-30% of patients with high-risk features who receive radiation recur with distant metastases.[9-14,16,20,21] Even patients treated with whole abdominal irradiation are at risk for extra-abdominal recurrences with progression-free intervals of 7 to 8 months.[24,25] Some randomized and retrospective studies have indicated that adjuvant radiation can be omitted in patients with stage I high-risk endometrial cancers.[26-29] However in all of these studies, patients who did not receive adjuvant radiation still had a considerably higher risk of recurrent disease, requiring salvage radiotherapy.[30]

Adjuvant chemotherapeutic regimens have been studied in high-risk endometrial cancers. Most have not demonstrated a survival advantage.[31-37] Platinum-based chemotherapies have a 13-42% response rate.[38-43] Combination chemotherapy with doxorubicin and platinum has upto a 43% response rate, but a high, and often prohibitive, toxicity profile.[44-50] Paclitaxel is an active agent in endometrial cancers and may have synergistic effects with radiotherapy.[51] Overall response rates with single-agent paclitaxel and docetaxel range from 30-36% in patients with advanced and recurrent endometrial cancer.[52-54] Paclitaxel combined with doxorubicin and cisplatin has been reported to increase overall survival by 3 months in patients with advanced endometrial cancers but at the risk of significant toxicity.[55,56] Paclitaxel and carboplatin combination therapy without radiation showed as acceptable toxicity profile and 40% response rate.[57]

Combination chemotherapy/RT trials have been performed on this group of patients through the RTOG (9708 and 9905).[16] Updated information from these trials have shown efficacy, but in light of the heterogeneous population, it is difficult do determine the true benefit for pure endometrial cancer patients. The regimen of RT followed by chemotherapy was well-tolerated in this patient population. No one has looked at the efficacy and toxicity of 'sandwich' therapy for pure high-risk endometrial cancer patients.

Our institutional experience with multi-modality treatment of another high risk uterine cancer, uterine papillary serous carcinoma (UPSC), is extensive. Since 1999, the Division of Gynecologic Oncology has been treating these patients with the "sandwich" protocol of combination chemotherapy and radiation therapy that is proposed for the current study. The UPSC data shows a three-year disease-free survival and overall survival with Stage I/II disease of 69% and 75% and Stage III/IV disease of 54% and 52%, respectively (unpublished data). These are better survival advantages than much of what is reported in the literature for this high-risk pathology.

In addition, the toxicity profile of this "sandwich" regimen was excellent, with neutropenia, thrombocytopenia, and anemia being the main grade 3 and 4 toxicities. 29 of the 30 patients completed the planned protocol treatment. The remaining patient was taken off study during RT due to noncompliance and recurred at seven months. Toxicity data is available for 177 cycles of the planned 180 cycles. Treatment cycles were grouped according to regimen received. Matched analysis of the total grade 3/ 4 toxicities after each cycle, demonstrated no difference in the number of toxic events between the platinum regimens or doses in either pre or post-RT chemotherapy cycles (p= 0.95 and p= 0.31, respectively). Grade 3/ 4 neutropenia, thrombocytopenia or anemia occurred in 42 %, 1% and 3% of cycles, respectively. Six cycles were delayed one week due to neutropenia, none of which were associated with fever. Grade 3 diarrhea occured in 1% of patients.

The optimal radiation modality, chemotherapeutic agents, and sequence of these regimens for the treatment of high-risk endometrial cancers are not yet well established. Therefore, we propose to study this combination of chemotherapy and radiation prospectively in patients with high-risk endometrioid-type endometrial adenocarcinomas.

However patients who are considered as high-risk stage I carries a different risk than those patients with stage II to stage IV disease. GOG 98 by Keys showed that patients with stage IB, IC and IIA (occult) and IIB (occult) disease receiving pelvic external beam radiation had a significantly less pelvic recurrence but similar overall survival rate to those who did not receive any treatment. [15] Recent publication by several European groups showed that vaginal radiation appeared sufficient in reducing regional recurrence without compromising their overall survival, especially in those who had complete staging procedure. In the Turkish study, 128 patients with Stage IA grade 3, IB grade 2, 3, and IC grade 1-3, and stage IIA or IIB had complete staging procedures, were given vaginal high dose radiation therapy.[59] The authors concluded that adjuvant vaginal brachytherapy was sufficient in treating this group of patients. In the ASTEC study, 905 patients with Stage IA, IB grade 3 tumor, IC any grade, clear cell or papillary serous carcinoma were randomized to no treatment versus radiation therapy.[60] Majority of the patients did not have any lymphadenectomy or sampling. Patient received 5-week of radiation therapy only. There were no difference in survival between the two groups. Majority of the recurrence was located along the vagina wall, suggesting that brachytherapy would be sufficient in treating this group of patients. In a smalle study from Washington University, patients with IA to II disease were randomized to brachytherapy only versus external beam plus brachytherapy.[61] A total of 78 patients enrolled in the study, and there were no difference in their overall survival. Due to these recent findings we feel that radiation therapy to the Stage I intermediate to high risk patients should consist of brachytherapy only in order to minimized the side effect and overtreatment of patients from radiation treatment. We believe that pelvic radiation therapy with external beam should continue due to its potential risks involved.

Finally, we plan to include a translational and basic science research component using patient tumor tissue. Recent data from our Division's research group suggests that hyperinsulemia may play a role in endometrial carcinogenesis. Based on the Women's Health Initiative (WHI), we conducted a prospective study of the associations of incident endometrial cancer with fasting

serum insulin, total and free IGF-1, and estradiol in post-menopausal women. We observed that endometrioid adenocarcinoma was significantly associated with high levels of insulin (HR 2.33, 1.13-4.82) and estradiol (HR 3.36, 1.91-5.91). We propose to study the associations of cancer recurrence with tumor tissue expression levels of IGF-I, IGF-II, IGFBP-1 and -3, insulin receptor, IGF-I receptor, estrogen receptor, and progesterone receptor. The protocol and systems to collect and store fresh tissue in concordance with patient protection measures has been previously implemented.

2.0 OBJECTIVES

2.1 To evaluate progression-free survival

2.1.1 To assess and document location of disease recurrence (distant vs. local. vs. both) using this treatment regimen.

2.2 To evaluate the toxicity of radiation therapy "sandwiched" between cycles of paclitaxel/carboplatin chemotherapy in patients with high-risk endometrial cancer: [paclitaxel/carboplatin (x 3 cycles)→ radiation therapy→ paclitaxel/ carboplatin (x 3 cycles)].

2.3 To evaluate the associations of cancer recurrence with tumor tissue expression levels of IGF-I, IGF_II, IGFBP-1 and -3, insulin receptor, IGF-I receptor, estrogen receptor, and progesterone receptor.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

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

1. Histologically-documented high-risk endometrioid adenocarcinoma with no visible residual disease, defined by the following criteria:
   a.

   d. Any surgical stage III disease (IIIA, IIIB, IIIC); and
   e. Any surgical stage IV disease with no residual macroscopic tumor

PORTEC-3 is a large randomized phase 3 trial that compared adjuvant chemoradiotherapy to radiotherapy alone for women with high risk endometrial cancer[67]. The recently published results showed no overall survival benefit to chemoradiotherapy when compared to radiotherapy alone for patients with stage I, II and III disease. There was a statistically significant difference in failure free survival for patients with stage III disease favoring chemoradiotherapy. Therefore, the authors concluded that chemoradiotherapy could not be recommended as the standard of care for patients with stage I or II endometrial cancer. For patients with stage III endometrial cancer, chemoradiotherapy can be considered to maximize failure free survival given the higher rates of recurrence in this group of patients.

In light of these results, providers at our institution have adapted these recommendations and are no longer recommending chemoradiotherapy for patients with high risk stage I and II endometrial cancer. Therefore, we would like modify the inclusion criteria for this study as above to keep with the new standard of care.

2. Surgical staging to include total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings, and lymph node samplings as per standard GOG criteria.
3. Age $\geq$ 18 years.
4. ECOG performance status of < 2.
5. 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/mm^3
   f. Absolute neutrophil count (ANC) < 1500/mm^3
   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 Un-controlled 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 dementia or altered mental status that would prohibit the giving and understanding of informed consent at the time of study entry.
5. 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.

4.0 REGISTRATION PROCEDURES

We plan on accruing 3 patients a year. 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 commercially available. Paclitaxel 175 mg/m^2 will be given over 3 hours in 250-500 ml of 5% dextrose or normal saline. Pre-medications for prevention of anaphylactoid reactions with anti-histamines and/or steroids should be administered as per standard practice.

Carboplatin is commercially available. Carboplatin at an AUC of 6.0 prior to radiation and AUC = 5 following radiation, should be administered following paclitaxel in approximately 250 ml of normal saline over 30 minutes. The initial GOG trial using combination taxol and carboplatin therapy was done on patients with optimally debulked ovarian epithelial carcinoma.[63] At that time Carboplatin dosing was done with an AUC of 7.5. Since then, multiple large cooperative trials have been performed using AUC of 6.0 and even 5.0. Despite the lower dosage of carboplatin, it didn't appear to compromise the efficacy of the drugs and should have an improved outcome in toxicity.[64-66] AUC based dosing as described by Calvert, *et al.*[58] will be according to the following formula:

- Dose (mg) = AUC x (GFR + 25),
- Where AUC is as stated above, and
- GFR is the calculated renal function according to the method of Cockroft and Gault: GFR (ml/min) = 0.85 for women x {(140-age)/Serum creatnine)} x {wt(kg)/72}. We will use serum creatinine of 0.8 as the lowest cut-off.

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 0.8 mg/dl in the GFR calculation for all patients whose creatinine is at or below 0.8 mg/dl. While this may be arbitrary, it minimize 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.

Chemotherapy must be given within 10 weeks of surgical staging. It 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 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.

5.1.2.1 Radiation therapy plan for stage I patients
For stage I patients, except stage IC, grade 3 patients, they will undergo high dose rate vaginal brachytherapy.

High Dose Radiation (HDR) brachytherapy involves a proximal 2/3 vaginal boost using the Nucletron Microselectron remote afterloading technique. Five fractions of 5 Gy each will be prescribed to 0.5cm depth from the vaginal cylinder surface. HDR will be given once a week for five weeks. The vaginal surface dose may be calculated at the vaginal surface lateral to the midpoint of the surface of the cylinder. A report on the dose to bladder and rectum is mandatory. The maximum dose to 2 cc volume of bladder and rectum are reported. The HDR treatment will be done as an outpatient in the radiation oncology suite.

5.1.2.2 Radiation therapy plan for all other subjects
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) or Intensity Modulated Radiation Therapy (IMRT) 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.

IMRT treatment will be prescribed and delivered according to the following specifications:

The vaginal planning target volume (PTV) and nodal PTV will receive 45 Gy in 25 fractions. Treatment will be delivered once daily, 5 fractions per week, over 5 weeks. All targets will be treated simultaneously. Breaks in treatment should be minimized. Total treatment breaks exceeding 5 consecutive days will be considered a major violation.

The Clinical Target Volume (CTV) is defined as areas considered to contain potential microscopic disease, delineated by the treating physician. The Planning Target Volume (PTV) will provide a margin around the CTV to compensate for the variability of treatment setup.

The nodal CTV should include lymph nodes that drain the involved site and adjacent perinodal soft tissue. This should include the internal (hypogastric and obturator), external, and common iliac lymph nodes; if the cervix is involved (even with endometrial cancer), presacral lymph nodes and soft tissues should be included as well, down to the level of S3. Identification of the CTV usually begins with the identification of the iliac vessels. The nodal CTV will include the vessel, perinodal tissue (on the pelvic wall side, the margin will exclude psoas and piriformis muscle) and pertinent clips. The average margin will be 7 mm. Bone and intraperitoneal small bowel should be excluded from the CTV; also, iliopsoas muscle that lies adjacent to clinically negative lymph nodes should also be excluded from the CTV. The most antero-lateral external iliac lymph nodes that lie just proximal to the inguinal canal should be excluded from the CTV (i.e., nodal CTV should stop right at the level of the femoral head). The CTV of the nodes should end at the L4/L5 interspace. If the para-aortic fields are added, the aorta and IVC are added to the nodal CTV up to the level of L1/2 with negative para-aortic or T10/11 with positive para-aortic nodes.

The vaginal and parametrial CTV should be included in PTV and it should encompass the vagina and paravaginal soft tissues. The inferior limit is usually around the level of the upper third of the symphysis pubis but can be individualized based on inferior spread of the patient's tumor on prior pre-operative physical examination and post-operative pathology reports. The lateral margin of the vaginal PTV should be to the obturator muscle. However, at least 3 cm of the vagina needs to be treated or at least 1 cm below the obturator foramen.

The Planning Target Volume (PTV) will provide a 7 mm margin (anteriorly, posteriorly, laterally, as well as in the superior and inferior directions) around the nodal CTV. The

vaginal PTV will be 10.0 mm around the vaginal ITV anteriorly, superiorly, inferiorly, laterally, and posteriorly.

Normal structures will be contoured from the CT scan.
Bladder – will be outlined on every slice, including the portion inferior to the planning target volume.
Rectum – will be outlined on every slice, including the portion inferior to the planning target volume and superior to the level that it leaves the posterior pelvis around the region of the rectosigmoid.
Small bowel – will be outlined on every slice, including at least 2 cm above the planning target volume. It includes the volume surrounding loops of small bowel out to the edge of the peritoneum because the bowel may lie within this space at any time throughout the course of treatment.
The femoral heads and the sacrum should be contoured in all slices.

For para-aortic treatment

Kidney – will be outlined entirely
Liver – will be outlined entirely
Spinal cord – will be outlined on every slice

The normal tissue constraints will be as follows:
Small bowel - Mean 30 Max 45 to 5%
Rectum - Mean 30 Max 45 to 25%
Bladder - Mean 36 Max 45 to 25%
Femoral head - Mean 40 Max 45 to 10%

For para-aortic treatment

Kidneys-15 Gy (33%) Max 45 to 10%
Liver - Mean 15, Max 45 to 10%
Cord - Max 45 Gy

The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose volume histogram (DVH) analyses of the PTV (CTV with a 7 mm margin) and critical normal structures. An inverse or forward-planning IMRT technique should be used. The treatment aim will be the delivery of radiation to the PTVs and the exclusion of non-involved tissues.

High Dose Radiation (HDR) brachytherapy involves a proximal 2/3 vaginal boost using the Nucletron Microselectron remote afterloading technique. Three fractions of 5 Gy each will be prescribed to 0.5cm depth from the vaginal cylinder surface. HDR will be given once a week for three weeks. The vaginal surface dose may be calculated at the vaginal surface lateral to the midpoint of the surface of the cylinder. A report on the dose to bladder and rectum is mandatory. The maximum dose to 2 cc volume of bladder and rectum are reported. The HDR treatment will be done as an outpatient in the radiation

oncology suite.

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. Antiemetic medications and hydration will be administered to prevent nausea and vomiting.

Toxicities particular to paclitaxel include hypersensitivity reactions and tissue damage from the infiltration of the diluent agent, CremaphorEL. Pre-medications (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. 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. Electrolytes will be monitored, and potassium and magnesium included in intravenous hydration to 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

Patients developing NCI Common Toxicity Criteria (CTC) grade 4 thrombocytopenia should have the carboplatin dose reduced by 25% on subsequent cycles. If this occurs on day 21, therapy should be withheld until counts return to an ANC > 1500/ul and platelet count > 100,000/ul. In the event of grade 4 neutropenia, paclitaxel should be administered with G-CSF or Neulasta on subsequent cycles beginning on day 2 and continuing until WBC > 10,000/ul.

If there is an interruption of more than one week, during chemotherapy or 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. Any patient requiring hospitalization while on protocol or any grade 4 hematologic or grade 3 or 4 non-hematologic toxicity will be reported.

All adverse events occurring during this clinical study must be reported to the principal investigator and accurately recorded 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 period from the 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 (See Appendix). 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. An ECG < 6 months prior to registration and laboratory tests will be obtained. Tests include the following: CBC with differential, platelet count, and serum chemistry (electrolytes, creatinine, BUN, glucose, magnesium, calcium, albumin, phosphorous, liver function tests).

Histologic documentation of high-risk endometrial pathology is required. Prestudy CA125, CA19-9, CT scan of chest, abdomen and pelvis (within 28 days of therapy), and CXR (if chest CT not available) will be obtained.

7.2 Tests During Treatment

Day 13-15 CBC with differential and platelet count

Every 3 weeks: CBC with differential, 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.

STUDY CALENDAR

Pamameter	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,	X		X	X	X

BUN, Cr					
SGOT, Bili	X		X	X	X
Urinalysis	X			X	X
CA-125, CA19-9	X		X	X	X
EKG	X				
CXR	X				X[2]
CT chest/abd/pelvis	X[1]			X	X[2,3]
Fresh Frozen Tissue	X				

1. Within 28 days of therapy
2. If clinically indicated.
3. Annually

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 CA125 and CA19-9. 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. Evaluation at each visit will include a complete history and physical examination and documentation of weight and performance status. Laboratory tests include a complete blood count with differential, platelet count, electrolytes, BUN, creatine, glucose, magnesium, calcium, phosphorous, albumin, CA125, CA19-9, and 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

Secondary endpoints include translational components that are yet to be confirmed.

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**:**

a. Paclitaxel

Other Names: Taxol, NSC 673089

Classification: Anti-microtubule 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®ELvehicle), 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.

b. 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 for women) x {(140-age)/Serum creatnine)} x {wt(kg)/72}.

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

The primary endpoint of the study is progression- free survival (PFS). PFS is defined as the time from randomization until documented tumor recurrence or death from any cause. PFS is censored at the date of the last follow-up visit for patients who are still alive and who have not progressed.

PFS will be analyzed using standard survival analytic methods, including the Kaplan-Meier approach for estimating the survival distribution. Median time to progression and 95% confidence intervals will be estimated from the Kaplan-Meier curves. Exploratory analyses will also be performed to evaluate the associations of PFS with tumor tissue expression levels of IGF-1, IGF-2, IGFBP-1 and IGFBP-3, insulin receptor, IGF-1 receptor, estrogen receptor and progesterone receptor. Provided the number of events is sufficient, Cox proportional hazards models will bit fit to the data to explore these associations.

For the purpose of assessing the adequacy of the proposed sample size of 40 patients (we will enroll up to 50 patients to obtain 40 with usable data. See Appendix I), we evaluated the precision with which the one-year progression free survival rate can be estimated. We project this rate to be 80% based on our institutional experience with multi-modality treatment of another high-risk uterine cancer (uterine papillary serous carcinoma). With 20 patients, the width of the 95% confidence interval for the true one-year progression free survival will be ± 17.5%. An early stopping rule will not be applied given that the primary endpoint is PFS and the limited number of patients that will be enrolled in this Phase II trial. We will also assess toxicity differences separate for the subgroup of patients who only receive vaginal brachytherapy as it is expected that this treatment will be less toxic.

As part of the analysis, a retrospective chart review of patients treated with this combination therapy off protocol will also be conducted. Individual charts will be reviewed and HIPAA unidentified epidemiologic, clinical, and surgical information will be obtained.

10.0 COLLECTION PROCEDURES

Translational and basic science research will be conducted on tissue from patients with high-risk endometrial cancer who consent to undergo further adjuvant treatment under this protocol. Since the final pathological grade of the tumor and the surgical stage will not be available till after the surgery, formalin-embedded tumor tissue will be obtained from the pathology archives at Montefiore Medical Center. The tissue cuts will be performed batched. Dr. Gloria Huang and her laboratory assistants will be responsible for the tissue procurement, storage, and further testing. Her laboratory phone number is (718) 430-2164.

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

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 high-risk endometrial cancer with no visible residual disease		
Surgical staging to include total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings, and lymph node sampling		
Pathology reviewed at MMC		
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 month, congestive heart failure, etc.)		
Patient has not had any prior chemotherapy or radiotherapy for pelvic malignancy.		
Patient does not have any history of cancer with the exception of non-melanoma skin cancer or evidence of any other malignancy within the last 5 years.		
Patients has no dementia or altered mental status that would prohibit the give and understanding of informed consent at the time of study entry.		

Patient Name_____

Patient MR#_____

Treating Physician_____

Principal Investigator_____
(Signature)

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Appendix I: Explanation on Increased Enrollment

We have enrolled 21 patients to this study between 2008-2014. The toxicity profiles of these patients have been assessed in an interim analysis. Baseline demographic data are as follows: the median age was 62. 66.7% (14/21) of the patients had stage I/II disease, while remaining 23.8% (7/21) had stage IIIC disease. 42.9% (9/21) had FIGO G1 disease, 23.8% (5/21) and 33.3 (7/21) had G2 and G3 disease. 66.7% (14/21) patients completed treatment per protocol. 76.2% (16/21) patients completed 6 cycles chemotherapy. 1 patient refused chemotherapy after enrollment. 4 patients could not complete chemotherapy due to hematologic toxicities.

Of 115 evaluable chemotherapy cycles, G3 or 4 combined hematologic toxicity events were as follows: 33/115 cycles (28.7%) neutropenia , 9/115 cycles (7.8%) thrombocytopenia, and 10/115 cycles (8.7%) anemia. Of 105 evaluable chemotherapy cycles, G3 or 4 combined non-hematologic events were as follows: 2/105 cycles (1.9%) infection, 1/105 cycles (0.95%) neuropathy, 4/105 (3.8%) metabolic, 1/105 (0.95%) venous thromboembolic. Dose reduction occurred in 6/115 cycles (5.2%) and dose delay in 12/115 cycles (10.4%). Since study onset, one of 21 recruited patients has recurred (lung) and died of disease.

Sequential sandwiched Chemotherapy radiation therapy is a tolerable treatment modality for patients with high risk endometrial cancer. Similar to other ‘sandwich’ protocols we have performed at Montefiore/Einstein, we anticipate there might be an additional progression-free and overall survival benefit for these high risk individuals. The 1 year progression-free survival rate to date of those patients treated on protocol is 95% (95% CI: 76.2% - 99.9%) . We conclude based on these pilot data that radiation “sandwiched” between T/P chemotherapy appears to be well tolerated and effective in improving DFS/OS in patients with completely resected high risk uterine cancers.

Given the acceptable toxicity rate observed thus far and high progression-free survival rates, we plan to increase the sample size of the study by 20 additional patients to a total of N=40 subjects to obtain more data on the toxicity and efficacy of this regimen and estimate event rates with greater precision. Specifically, assuming that the observed 1 year-PFS rate continues to be 95%, the width of the 95% confidence interval for the true one-year progression free survival will be (83% - 99.4%) with 40 patients