A Pilot Safety and Toxicity Trial of Adjuvant Chemotherapy with Gemcitabine and Docetaxel and Radiation Therapy for completely resected Uterine Leiomyosarcoma

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SCHEMA

Weeks 1-12
Gemcitabine 900mg/m2/90 min days 1, 8 & Docetaxel 75mg/m^2/1 hour day 8
Repeat q 21 days x 4 cycles

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Weeks 10-12
High Dose Rate (HDR) Brachytherapy x 3, or IMRT where appropriate
Nucletron Microselectron Afterloading Technique
5 Gy to 0.5cm Depth from the Vaginal Cylinder Surface
Total Dose 15 Gy

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Weeks 13-17
Pelvic +/- Para-aortic External Beam Radiation Therapy
1.8 Gy Dose/Fx
Total Dose 45Gy

1.0 BACKGROUND

Leiomyosarcoma is the most common form of sarcoma of the uterus, but accounts for only 2-3% of all cancers of the uterine corpus [1]. Leiomyosarcomas are characterized by early hematogenous spread. Even those patients who present with early stage disease have recurrence rates of 53 to 71% [1]. Five-year survival rates for Stage I (confined to the uterus) is 50%, quickly dropping off to 25% for those with Stage II (pelvic spread), and essentially 0% for those with Stage III/IV [2] .

Like with most sarcomas, optimal surgical resection provides the most benefit to patients in terms of disease control and overall survival [3]. However, adjuvant therapy is clearly needed given the high recurrence rates and poor prognoses. No specific adjuvant treatment has emerged as the standard of care. Given the fact that 40% of first recurrences are diagnosed in the lungs, chemotherapy would seem to be a rational choice for adjuvant therapy as it offers systemic delivery [1]. Currently, no standard chemotherapy regimens exist either in the adjuvant or advanced/recurrent settings. Also, there are limitations in the existing literature. Few randomized, controlled trials exist because of the low incidence of uterine leiomyosarcoma. Many trials have pooled together all uterine sarcomas, including carcinosarcomas which are now classified as epithelial tumors, and those who have been able to do a subset analysis have demonstrated that there are differences in the behaviors and responses of leiomyosarcomas from other forms of sarcoma. Other trials have extrapolated from all leiomyosarcomas, not just those originating in the uterus.

CHEMOTHERAPY

While many agents have been tested, few have been found to have efficacy against uterine leiomyosarcoma [4]. Currently, the most commonly used regimen for treatment of recurrent or advanced/unresectable uterine leiomyosarcoma had been the combination of doxorubicin with ifosfamide. In a phase III trial for uterine sarcomas, the subset of subjects with advanced leiomyosarcoma demonstrated a 25% response rate to a doxorubicin 60mg/m2 dose [5]. The addition of ifosfamide 1g/m2 to doxorubicin 50mg/m2 was evaluated in a phase II trial of advanced uterine leiomyosarcoma and demonstrated a 30% response rate, albeit at the expense of nearly half of the patients getting a grade 3 and 4 neutropenia [6]. While not compared against single-agent doxorubicin in a trial, the combination became the most commonly used regimen based on this data. Recently, single-agent liposomal doxorubicin was assessed in a phase II trial and showed only a 16% response rate, seemingly inferior to doxorubicin although not compared in a head-to-head fashion [7].

More recently, treatment studies have shown the combination of gemcitabine and docetaxel to be promising. A phase II trial for patients with unresectable leiomyosarcoma was conducted using the combination of gemcitabine 900mg/m2 on day 1 and 8 and docetaxel 100mg/m2 for up to 8 cycles with a 25% dose-reduction for patients with prior pelvic radiation [8]. The trial included all leiomyosarcomas, although 85% were of uterine origin. Furthermore, patients were eligible for up to two prior chemotherapies, and almost half had been pre-treated with a doxorubicin-based treatment. Prophylactic granulocyte-colony stimulating factors were given with each cycle. The overall response rate was 53%. Patients who had received prior doxorubicin-based therapy did not show any significant difference in response than

those who had not. While single-agent docetaxel and gemcitabine had shown responses inferior to doxorubicin, the combination of the two agents results in a synergy that makes it as one of the most active drug combinations studied to date [8].

This study of patients with advanced stage unresectable disease led to the evaluation of gemcitabine/docetaxel in the adjuvant setting following surgical resection to decrease the high rate of recurrence. A single-institution trial of gemcitabine 900mg/m2 on day 1 and 8 and docetaxel 75mg/m2 with GCSF support for 4 cycles found a 45% 2-year progression-free survival [9]. The subset analysis of the 15 patients with Stage 1 disease and 3 with Stage 2 disease demonstrated a 59% 2-year progression-free survival. The overall survival at 5 years was around 60%, compared to the historical 50% overall survival for Stage 1 disease found in the large Norwegian study [2]. Furthermore, the regimen was associated with very acceptable toxicity that was found to be lower than the prior trial for those with unresectable leiomyosarcoma.

RADIATION THERAPY

There were several retrospective studies of uterine sarcomas that suggested prevention of local recurrence after adjuvant radiation therapy (RT), with no additional survival benefit. In those studies, benefit was usually limited to carcinosarcoma or endometrial stromal sarcoma. These early studies led to a prospective, randomized-controlled trial that was performed to assess the benefit of adjuvant RT in leiomyosarcoma [10]. After surgery, stage I/II patients were randomized to receive 50 Gray of external beam in 28 fractions over 5 to 6 weeks or not to receive any radiation therapy. While there was a decrease in the rate of recurrence in the carcinosarcoma patients who received RT, there was no difference in the recurrence rates in the leiomyosarcoma patients when compared to no RT. This study also revealed that the rate of distant recurrence for leiomyosarcoma was 25%, more than twice that for carcinosarcoma. While there was a trend towards decreased local recurrence, this study discredited the idea that achieving local control would reduce the rate of distant metastases and did not impact overall survival.

In order to try to prevent both distant and local recurrence, the concept of using both chemotherapy and RT following surgical resection was evaluated in a small prospective trial with 13 stage I/II optimally cytoreduced leiomyosarcoma patients who received adriamycin, cisplatin, and ifosfamide every 3 weeks for 3 cycles followed by external beam pelvic radiation and, for some, brachytherapy [11]. Of the 5 patients that recurred, none had pelvic recurrences, and the overall 2-year survival was 78%.

A larger study using a multimodal approach is necessary to assess the efficacy and toxicity associated with chemotherapy and radiation therapy. Furthermore, given the recent data suggesting the gemcitabine and docetaxel combination as having superior activity than some of the older doxorubicin-based treatments, a regimen containing these two drugs would be ideal to use in the adjuvant setting with radiation therapy.

At Montefiore, we have performed a number of sequential chemotherapy and RT trials in high risk uterine cancers using various doublets with full EBRT and brachytherapy [12-14]. Given the limitations of either chemotherapy alone or RT alone, we think the combination of both for early stage leiomyomsarcoma in an adjuvant setting might hold promise. Our experience in patients with other high risk

uterine cancers with larger doses and more cycles of chemotherapy and RT has confirmed predictable toxicities that are manageable. This trial is designed to assess the safety and tolerability of sequential gemcitabine and docetaxel, the current optimal regimen for leiomyosarcoma, followed by RT to limit pelvic recurrences.

2.1 OBJECTIVES

2.2 Primary Objective: To evaluate the toxicity and tolerability of adjuvant pelvic radiation in combination with gemcitabine/docetaxel chemotherapy in patients with stage 1 and 2 surgically-resected uterine leiomyosarcoma.

2.3 Exploratory Objective: To assess the two year recurrence-free survival in patients with uterine leiomyosarcoma treated with chemotherapy and radiation therapy including defining the patterns of recurrence in patients with uterine leiomyosarcoma who were treated with this regimen.

3.1 PATIENT SELECTION

3.2 Inclusion Criteria

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

a. Histologically documented uterine leiomyosarcoma with no visible residual disease.

b. Surgical staging to include total hysterectomy, +/- removal of ovaries and fallopian tubes, +/- lymph node sampling.

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.

3.3 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. Patients with severe or uncontrolled concurrent medical disease (eg. uncontrolled diabetes, unstable angina, myocardial infarction within 6 months, congestive heart failure, etc.)
3. Patients with any prior chemotherapy or radiotherapy for pelvic malignancy.
4. Patients who have had prior therapy with gemcitabine or docetaxel.
5. Patients with known hypersensitivity to gemcitabine or docetaxel.
6. Patients with known hypersensitivity to Pefilgrastim and Filgrastim.
7. 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.
8. 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.

5.1 TREATMENT PLAN

5.2 Chemotherapy

5.2.1 Gemcitabine, Gemzar® is commercially available. Gemcitabine 900 mg/m2 on days 1 and 8 will be given intravenously over 90 minutes.

5.2.2 Docetaxel, Taxotere® is commercially available. Docetaxel 75 mg/m2 will be given intravenously on day 8 over one hour following gemcitabine. Premedication for Docetaxel for the prevention of severe fluid retention and hypersensitivity reaction is as follows: Dexamethasone 8 mg orally x 2 doses the day prior to chemotherapy (day 7), and 8mg orally twice daily for the next 2 days (days 8-9). The dexamethasone dosing schedule may be adjusted per the discretion of the physician. Patients who develop peripheral edema as a side effect of docetaxel may be treated with diuretics at the discretion of the treating physician. Recommended treatment for edema includes starting with Dyazide (25/37.5) or (25/50) up to three times per day. Furosemide may be used if Dyazide does not adequately control the edema.

5.2.3 Pegfilgrastim, Neulasta® is commercially available. Pefilgrastim, granulocyte-colony stimulating factor, will be given as a subcutaneous injection of 6 mg on day 9.

Chemotherapy will be administered every 21 days for 4 cycles. This will be followed by radiotherapy.

5.3 Radiotherapy

HDR vaginal cuff brachytherapy or Intensity Modulated Radiation Therapy (IMRT) vaginal cuff boost when brachytherapy is not feasible will begin with the 4th cycle of chemotherapy (week 10). HDR brachytherapy, or Intensity Modulated Radiation Therapy (IMRT) where appropriate, involves a proximal 1/2 - 2/3 vaginal boost using the Nucletron microSelectron remote afterloading technique. The vaginal boost may be extended to include the distal vagina when gross vaginal involvement is present. Three fractions of 5 Gy each will be prescribed to 0.5cm depth from the vaginal cylinder surface. Three doses of HDR will be completed prior to beginning external beam irradiation.

For HDR and IMRT, a report on the dose to bladder and rectum is mandatory. A 3-dimensional CT scan will be obtained with the applicator in place for brachytherapy planning. The brachytherapy plan will be made on the Nucletron Oncentra software using the planning CT, and dose-volume histograms will report the bladder and rectal dose levels. The vaginal surface dose may be calculated at the vaginal surface lateral to the midpoint of the surface of the cylinder.

The patient will commence external beam radiation therapy (EBRT) after completion of brachytherapy (week 13). The total dose of EBRT 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 3-dimensional conformal technique (AP-PA opposed and lateral opposed fields) or an IMRT technique will be used with a megavoltage beam of ≥ 6MV. The fields may be extended to include the para-aortic lymph nodes in the case of ≥ 2 positive pelvic nodes or documented para-aortic lymph node disease.

Pretreatment CT scan of the abdomen and pelvis will be used for planning. Full and empty bladder scans will be performed in preparation for creation of an ITV for planning purposes. Oral contrast will be given prior to the CT, and vaginal contrast placed at the time of simulation to help identify internal anatomy. All fields treated require portal verification on the treatment unit. 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 L4 and L5; a lateral border 1.5-2.0 cm lateral to the widest true pelvic diameter; and an inferior border at the bottom of 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 superior and inferior borders 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.

Para-aortic Portal: Includes a superior border of T11-T12 or 3 cm superior to the positive node site; an anterior border 2-3 cm anterior to the vertebral body; lateral borders 2-3 cm lateral to the vertebral body; and a posterior border that will exclude the spinal canal.

5.4 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 for evidence of toxicity. Antiemetics and hydration will be administered to prevent nausea and vomiting.

Toxicities particular to Docetaxel include hypersensitivity reactions and fluid retention. Premedication for the prevention of severe fluid retention and hypersensitivity reaction is as follows: Dexamethasone 8 mg orally x 2 doses the day prior to chemotherapy (day 7), and 8mg orally twice daily for the next 2 days (days 8-9). The dexamethasone dosing schedule may be adjusted per the discretion of the physician. Patients who develop peripheral edema as a side effect of Docetaxel may be treated with diuretics at the discretion of the treating physician. Recommended treatment for edema includes starting with Dyazide (25/37.5) or (25/50) up to three times per day. Furosemide may be used if Dyazide does not adequately control the edema. Premedications with diphenhydramine and H2 blockers will be added 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 infusion site reactions can occur.

Toxicities particular to Gemcitabine include hematologic (anemia, thrombocytopenia, neutropenia), and gastrointestinal (nausea and vomiting). Premedication with anti-emetics on day 1 and day 8 will be given to reduce the incidence and severity of nausea and vomiting. The administration of Pefilgrastim on day 9 appears to reduce the incidence and severity of neutropenia. Complete blood counts will be monitored for evidence of toxicity.

Toxicities particular to Pefilgrastim include transient bone pain that can be controlled with non-narcotic analgesics and transient increases in alkaline phosphatase, lactate dehydrogenase and uric acid that will be monitored with each cycle.

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. While unlikely, in order to minimize the potential for radiation recall effects, external beam radiation will begin three weeks after the last cycle of chemotherapy (two weeks after the last dose of gemcitabine) [15].

5.5 Treatment Modifications

Dose reductions of one dose level equate to 25% reduction of prior dose:

Drug	100% Dose	25% Dose Reduction
Gemcitabine	900mg/m2	675mg/m2
Docetaxel	75mg/m2	56mg/m2

5.5.1 Hematologic Toxicity:

5.4.11 Initial treatment modifications will consist of cycle delay and/or dose reduction as indicated below.

Patients will NOT receive prophylactic thrombopoietic agents unless they experience recurrent grade 4 thrombocytopenia after treatment modifications as specified below.

Patients may receive erythropoietin for management of anemia after documentation of hemoglobin less than 10 g/dL (CTC grade 2).

5.4.12 For patients who experience febrile neutropenia, a platelet count of <10,000/microliter or CTC grade 3 associated with bleeding or platelet transfusion, and/or documented grade 4 neutropenia persisting ≥ 7 days, the doses of both gemcitabine and docetaxel will be reduced by 25% of the prior dose for all subsequent cycles for that patient.

5.4.13 All Day 1 chemotherapy will be held pending hematologic recovery to ANC ≥ 1000/microliter and platelet count greater than or equal to 100,000/microliter. Due to patients receiving G-CSF, day 1 of cycle may be given with ANC ≥ 1000 cells/uL, to allow for transient reductions in ANC after discontinuation of G-CSF. Patients in whom counts have not recovered after a 2 week delay will be removed from the study.

5.4.14 Day 8 dose adjustments should be made according to the table below

Drug	ANC≥1000 and Plt ≥100,000	ANC 500-999 or Plt 50-99,000	ANC <500 or Plt <50,000
Gemcitabine	900mg/m2	675mg/m2	Omit
Docetaxel	75mg/m2	56mg/m2	Omit

5.5.2 Hepatotoxicity: If bilirubin is greater than institutional upper limits of normal on day 1, repeat level on day 8 prior to giving Docetaxel. If bilirubin has returned to normal, then proceed with administration of Docetaxel on day 8. If bilirubin remains greater than institutional upper limits of normal on day 8, then give only gemcitabine. If bilirubin does not recover by day 8 of the next cycle, the patient will be removed from study due to hepatic dysfunction. Grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), or alkaline

phosphatase requires dose reduction of 25% and delay in subsequent therapy for a maximum of 14 days until recovered to grade 1.

5.5.3 Neurotoxicity: For grade 3 or 4 neurotoxicity, treatment will be delayed 1 week. At the time of re-evaluation, if neurotoxicity is ≤ grade 2, then the patient may continue on study with subsequent docetaxel dose reduction of 25%. If the grade 3 or 4 neurotoxicity has not resolved to ≤ grade 2 after one week delay, the patient will be removed from study. Grade 2 or greater peripheral neuropathy requires dose reduction of 25% and a delay of subsequent cycles for a maximum 14 days until recovered to grade 1.

5.5.4 Nephrotoxicity: Grade 2 or greater renal toxicity requires dose reduction of 25% and a delay of subsequent cycles for a maximum of 14 days until recovered to grade 1.

5.5.5 Patients who develop grade 4 edema will be removed from study.

5.5.6 Other non-hematologic toxicities that are grade 2 or greater, with an impact in organ function will require dose reduction of 25% and a delay of subsequent cycles for a maximum of 14 days until recovered to grade 1 or to pre-therapy baseline.

5.5.7 Radiation Recall: In the event of signs or symptoms of radiation recall effect, Topical or systemic corticosteroids or nonsteroidal anti-inflammatory agents can be used to decrease signs or symptoms of inflammation [16]. Antihistamines may be used for symptomatic relief. These supportive measures can be used at the discretion of the provider. Re-challenge can be performed with premedication with corticosteroids and a 25% dose reduction of the offending chemotherapeutic agent or the dose per fraction of radiation.

Grade 2 or greater radiation recall will require a delay in chemotherapy and/or radiation therapy for one week. Then the patient will be re-evaluated. If the effects are persistent, the patient will undergo another week of delay for a maximum of 14 days. If the effects continue, the patient will be withdrawn from study and undergo exit visit procedures.

5.6 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 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 MEASUREMENT OF EFFECT

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.

8.1 STUDY PARAMETERS

8.2 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. 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 leiomyosarcoma is required. Prestudy CT scan of chest, abdomen and pelvis (within 28 days of therapy), and CXR (not required if CT of the chest) will be obtained.

8.3 Tests During Treatment

Day 8: CBC with differential and platelet count, liver function tests if needed as described in section 5.4.2

Every 3 weeks (prior to each cycle of chemotherapy): CBC with differential and platelet count electrolytes, BUN, creatinine, glucose, magnesium, calcium, phosphorous, albumin, liver enzymes and liver function tests (AST, ALT, alkaline phosphatase, bilirubin).

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

8.4 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, and urinalysis.

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

8.5 Follow-up

Patients will be evaluated as per the current standard of care which is every 3 months for the first 2 years and every 6 months for the next 3 years. Evaluation at each visit is as per the current standard of care which 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, and urinalysis. CT scans will be performed annually or earlier if clinically indicated. After a total of 5 years, patients will be seen annually.

8.6 Secondary Endpoints

Staining of the pathologic specimens for ER/PR, will be performed by immunohistochemisty and will be correlated with progression-free survival and prognosis.

8.7 Discontinuation

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

9.1 DRUG FORMULATION AND PROCUREMENT

9.2 Drug Information**:**

Docetaxel

Other Names: Taxotere, NSC 628503

Classification: Belongs to the class of plant alkaloids and other natural products, taxanes.

Mechanism of Action: It is an antimicrotubule agent. It promotes and stabilizes microtubule assembly, while preventing physiological microtubule disassembly thus preventing mitotic cell division and initiating apoptosis.

Storage and Stability: 20 mg vials may be stored for 24 months below 25°C away from light and 80 mg vials for 26 months in the same conditions. Freezing does not adversely affect the product. Premixed Docetaxel solutions should be used within 4 hours.

Route of Administration: Intravenous
A single dose vial must be combined with the dilutent (13% ethanol in water for injection) to obtain a premixed solution of Docetaxel 10mg/mL. Then withdraw the desired amount of Docetaxel and dilute it in a 250 mL infusion bag containing normal saline or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final Docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Dose Specifics: Docetaxel is given at a dose of 75-100 mg/m2 infused over one hour and repeated every 21 days. All patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (8 mg BID) for 3 days starting one day prior to Docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

Drug Interactions: Cisplatin is known to interact with some CYPs and has in some cases been shown to reduce Docetaxel clearance by up to 25%, which may increase myelosuppression. Erythromycin, ketoconazole and cyclosporine are CYP3A4 inhibitors and therefore inhibit the metabolic pathway of Docetaxel. Anticonvulsants induce some metabolic pathways relevant to Docetaxel.

Adverse Effects Profile: Neutropenia, thrombocytopenia, anemia, alopecia, injection sites reactions, rash, nausea, vomiting, mucositis, typhlitis, increased liver enzymes, hepatic failure, sensory changes, peripheral neuropathy, arthralgia and myalgia, mood alterations, motor and autonomic neuropathy, hypersensitivity, fluid retention, cardiac dysrythmias, syncope, hypotension, myocardial infarction, hypertension. Other: fatigue, headaches, light-headedness, myopathy, elevated serum creatinine, elevated serum triglycerides, and visual abnormalities.

Supplier: Commercially available.

Gemcitabine

Other Names: Gemzar®, NSC 613327

Classification: Antimetabolites, pyrimidine analogs.

Mechanism of Action: Inhibition of DNA synthesis by inhibition of ribonucleotide reductase.

Storage and Stability: Gemcitabine is supplied in 200 mg (10mL) and 1000 mg (50mL) sterile single use vials. Unopened vials of Gemcitabine are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F).

Route of Administration: Continuous infusion over 90 minutes.
Gemcitabine is reconstituted by adding 5 or 25 mL of injectable normal saline to the 200-mg or 1-gram vial, respectively, creating a concentration of 38mg/mL of Gemcitabine. The resultant solution is a clear, colorless to light straw-colored solution. Incomplete dissolution may occur if Gemcitabine is reconstituted to a concentration greater than 40 mg per mL. The resulting solution may be further diluted with injectable normal saline, if necessary, to a concentration as low as 0.1 mg per mL. Once the drug has been reconstituted, it should be stored at controlled room temperature and used within 24 hours.

Dose Specifics: 600-1250 mg/m2

Drug Interactions: Gemcitabine may alter the pharmacodynamic response to warfarin resulting in an increased INR and risk of bleeding.

Adverse Effects Profile: Neutropenia, thrombocytopenia, anemia, rash, mild alopecia, nausea, vomiting, diarrhea, constipation, stomatitis, dyspnea, fever, irritation, pain or redness at the injection site increased liver enzymes, reversible proteinuria, elevation of BUN and creatinine, edema, bronchospasm, pareshesia, somnolence cerebrovascular accident, myocardial infarction, dysrythmia. Other (rare): hemorrhage, allergic reaction, pneumonitis, pulmonary edema, hemolytic uremic syndrome.

Supplier: Commercially available.

Pegfilgrastim

Other Names: Neulasta®, NSC 725961

Classification: Granulocyte colony stimulating factor

Mechanism of Action: Acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.

Storage and Stability: Pegfilgrastim should be refrigerated between 2° to 8°C (36° to 46°F) in the carton to protect from light. Do not shake. Discard syringes stored at

room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

Route of Administration: Subcutaneous injection.
Pegfilgrastim is supplied in 0.6 mL pre-filled single use syringes for subcutaneous injection. Each syringe contains 6 mg Pegfilgrastim (based on protein weight), in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), sorbitol (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP.

Dose Specifics: 6 mg

Drug Interactions: No formal drug interactions studies have been done with Pegfilgrastim.

Adverse Effects Profile: Bone pain, reversible elevations of alkaline phosphatase, lactate dehydrogenase and uric acid, allergic reactions including anaphylaxis, urticaria, severe sickle cell crisis in sickle cell patients, ARDS. Other (rare): splenic rupture.

Supplier: Commercially available.

10.0 STATISTICAL CONSIDERATIONS

To assess the two year recurrence-free survival in patients with uterine leiomyosarcoma treated with a combination of chemotherapy and radiation therapy - including defining the patterns of recurrence in patients with uterine leiomyosarcoma who were treated with this regimen. A total of 18 patients will be accrued to this study. Two-year recurrence-free survival probability will be estimated, with 95% confidence limits based on exact methods for the binomial distribution. In the event of censoring before two years, a Kaplan-Meier estimate of the survival probability will be used and a Kaplan-Meier survival curve will be estimated and presented as well. 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.

11.0 COLLECTION PROCEDURES

Paraffin embedded tissue from uterine leiomyosarcoma tumors will be stained for ER/PR, by immunohistochemistry.

12.0 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

13.0 PATIENT CONSENT AND PEER JUDGEMENT

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

14.0 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.

15.0 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.

16.0 DATA SAFETY MONITORING PLAN

This study will be added to the Montefiore Einstein Cancer Center Date Safety Monitoring Committee's (DSMC) agenda for internal study review. As per the DSMC protocol, all adverse events will be forwarded to the DSMC, and monitored on a monthly basis.

17.0 ELIGIBILITY CHECKLIST

	Yes	**No**
Histologically documented uterine leiomyosarcoma with no visible residual disease		
Surgical staging to include total abdominal hysterectomy, +/- bilateral salpingo-oophorectomy, +/- 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)

18.0 REFERENCES

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APPENDIX 1: STUDY SCHEDULE

Parameter	Pre-treatment	Day 8 (Cycles 1-4)	Each Cycle	Completion of Study	Follow-up Visit
History & Physical Exam	X		X	X	X
Pelvic Exam	X		X	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
CXR	X[4]				X[1]
CT chest/abd/pelvis	X[3]			X	X[2,1]
ER/PR	X				

1. If clinically indicated.
2. Annually
3. Within 28 days of therapy
4. CXR not needed if CT chest performed