Study Title
The SACS trial - Phase II Study of Adjuvant Therapy in CarcinoSarcoma of the Uterus

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Study Plan
A prospective single-arm phase II study of adjuvant therapy, consisting of two cycles of Carboplatin and Abraxane followed by radiotherapy delivered with concurrent Cisplatin, then a further two cycles of Carboplatin and Abraxane, in patients with FIGO stage IA (with myometrial invasion) to IVA (excluding stage IIIC2) carcinosarcoma of the uterus

Aim
This study aims to investigate the feasibility, efficacy and toxicity of a combined regimen of radiotherapy and chemotherapy for patients with carcinosarcoma of the endometrium.

Background and Significance
Carcinosarcoma is an uncommon malignancy, with approximately 10-20 cases per year in Victoria, most of which are localised disease. This tumour has an aggressive biology with patients being at high risk of both local and distant disease recurrence following surgery. Adjuvant pelvic radiotherapy is often used to reduce the risk of local disease recurrence. Due to the high risk of distant disease recurrence, multiple institutions have trialled combined treatment regimens consisting of adjuvant radiotherapy and adjuvant chemotherapy. In 2002, Manolitsas et al found that patients treated with a 'sandwich' regimen (two to three cycles of Epirubicin and Cisplatin then radiotherapy then a further two to three cycles of Epirubicin and Cisplatin) had an overall survival rate of 74% (mean duration of follow-up of survivors of 55 months). In the last decade, taxanes have become standard of care in the treatment of other gynaecological malignancies and have been increasingly prescribed for patients with carcinosarcoma. This trial aims to prospectively investigate the feasibility efficacy and toxicity of a 'sandwich' regimen of combined adjuvant therapies, using modern chemotherapy agents.

Hypotheses
- "That the combined regimen (two cycles of Carboplatin and Abraxane followed by radiotherapy with concurrent Cisplatin chemotherapy then two further cycles of Carboplatin and Abraxane):
    - Will be feasible
    - Will be well tolerated
    - Will result in superior overall survival compared to historical outcomes achieved with adjuvant radiotherapy alone or with combined adjuvant regimens using older chemotherapy agents."

Primary Objective

- To evaluate the feasibility of two cycles of Carboplatin and Abraxane followed by radiotherapy delivered with concurrent Cisplatin, then a further two cycles of Carboplatin and Abraxane, in patients with FIGO stage IA (with myometrial invasion) to IVA (excluding stage IIIC2) carcinosarcoma of the uterus

Secondary Objectives

- To evaluate the efficacy of the treatment protocol as measured by time to local, loco-regional and distant recurrence, failure-free survival and overall survival

- To evaluate the safety and tolerability of the treatment protocol as measured by the incidence and severity of acute and late toxicity

Schema

Surgery consisting of TAH/TLH, BSO, washings, omentectomy (if carcinosarcoma diagnosis known pre-operatively) +/- pelvic lymph node dissection

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PET-CT scan (CT C/A/P if PET-CT unavailable), Blood tests (FBE, U+E, LFT, Ca), Tests to assess suitability for chemotherapy

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Eligible patients invited to participate in trial. Patients who provide consent enrolled.

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2 x cycles of Carboplatin and Abraxane chemotherapy

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Radiotherapy with concurrent Cisplatin chemotherapy

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2 x cycles of Carboplatin and Abraxane chemotherapy

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Follow up, consisting of:

1. Clinical review at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 48, 60 months post treatment
2. Repeat PET/CT scan (CT C/A/P if PET-CT unavailable) at 6 months post treatment

Inclusion Criteria

- The patient must have a newly diagnosed, histologically confirmed carcinosarcoma of the uterus, with myometrial invasion corresponding to FIGO stage IA (with myometrial invasion), IB, II, III (IIIC2 excluded) or IVA disease. Patients with involved lymph nodes meet inclusion criteria if lymph nodes are located below the pelvic brim (the presence of para-aortic lymph nodes is an exclusion criteria).
- The patient must have undergone a total abdominal hysterectomy and bilateral salpingo-oophorectomy with or without a dissection of pelvic and/or para-aortic lymph nodes.
- Staging PET/CT or CT Chest/Abdomen/Pelvis must reveal no residual disease above the external iliac lymph nodes
- ECOG performance status 0-2
- Life expectancy > 6 months
- Absolute neutrophil count ≥1,500/μl
- Platelets ≥100,000/μl
- Total bilirubin <1.25 upper limit of normal
- AST (SGOT)/ALT (SGPT) ≤3 x institutional upper limit of normal
- Estimated GFR ≥50ml/min
- Patients must provide written consent

Exclusion Criteria

- Surgery or post-operative PET-CT (or CT C/A/P if PET-CT unavailable) reveals any disease outside the pelvis, except for +ve peritoneal washings.
- The patient is receiving any another investigational agent
- The patient has an existing symptomatic peripheral neuropathy ≥ grade 2
- The patient has a past history of invasive malignancy (except for non-melanomatous skin cancer) within the preceding five years
- The patient has a past history of allergy to carboplatin or taxane-based chemotherapy
- The patient has a serious illness or medical condition that precludes safe administration of trial treatment
- The patient has a past history of radiotherapy treatment to the pelvis
- The patient has a past history of inflammatory bowel disease
- The patient is unable to provide informed consent

Study Treatment

Patients will be referred after surgery and histopathological confirmation of diagnosis

Eligible patients will be treated with adjuvant therapy as follows:

Chemotherapy administration:

- Timing: Chemotherapy will commence as soon as is practicable after surgery, in keeping with standard practice
- Regimen
  - Two cycles of Carboplatin (AUC 6) and Abraxane (260mg/m2) q21 days
  - Cisplatin 40mg/m2 weekly x 5 delivered concurrently with radiotherapy
  - Two cycles of Carboplatin (AUC 5) and Abraxane (260mg/m2) q21 days to commence 3-6 weeks after completion of all radiotherapy treatments

Radiotherapy administration:

- Timing: Radiotherapy will commence 3-6 weeks following the second cycle of adjuvant Carboplatin and Abraxane
- Regimen:

Whole pelvic radiotherapy 45Gy/25Fx, +/- boost to vaginal vault if cervical stromal involvement or if close/positive margins (boost may be delivered with external beam radiotherapy to a total dose of 50.4-54Gy or via an HDR brachytherapy boost to the superior 3-4cm of the vaginal vault to a dose of 10Gy in 2Fx prescribed to 5mm) +/- boost to involved lymph nodes (to a total dose of 50.4-54Gy). The total treatment time for all radiotherapy treatment should not exceed eight weeks.

Statistical Considerations

Endpoints

The primary end-point to assess feasibility will be:

- The number of participants who are able to complete ≥ 80% of protocol treatment in ≤ 125% of the scheduled treatment timeframe
    - The protocol will be considered feasible if a minimum of 75% of participants are able to complete ≥ 80% protocol treatment in ≤ 125% of scheduled treatment timeframe

The following secondary endpoints will be defined in order to address the secondary objective of efficacy:

- Time to local recurrence, measured from the date of commencement of treatment until the date of vault or any vaginal recurrence
- Time to loco-regional recurrence, measured from the date of commencement of treatment until the date of pelvic lymph node recurrence or other pelvic recurrence (excluding vault or any vaginal recurrence)
- Time to distant recurrence measured from the date of commencement of treatment until the date of any of the following: para-aortic nodal recurrence, retroperitoneal recurrence, liver, lung, bone, other distant metastatic site recurrence
- Failure-free survival measured from the date of commencement of treatment until local, loco-regional or distant recurrence or death from any cause.
- Overall survival measured from the date of commencement of treatment until death from any cause

The following secondary endpoints will be defined in order to address the secondary objective of safety and tolerability:

- Incidence and worst grade of acute and late adverse events. Acute events are defined as those experienced during treatment and up to three months following completion of treatment. Late events are defined as those experienced after a three month time period has lapsed following completion of treatment.

Sample size and expected study duration

A pragmatic sample size of 50 eligible patients will be accrued for this study. This sample size is considered large enough to provide useful estimates of the feasibility and tolerability of a combined regimen of radiotherapy and chemotherapy for patients with carcinosarcoma of the endometrium.

For the secondary time-to-event endpoints, this sample size of 50 eligible patients will enable yearly recurrence and survival rates to be estimated with a maximum 95% confidence interval width of +/– 14%.

It is expected to take approximately 3 years to accrue the target number of 50 eligible patients. Treatment with the combined radiotherapy and chemotherapy regimen will take approximately 6 months and patients will be followed up for a minimum of 3 years following completion of treatment. The study duration is therefore expected to be 6.5 years.

Statistical analysis

For feasibility and efficacy endpoints, all eligible patients will be included in an intent-to-treat (ITT) analysis. For safety endpoints, the evaluable patient population will include all eligible patients who commenced protocol treatment.

The main analysis of the primary objective will take place once all 50 eligible patients have been accrued and completed treatment. The final analysis of time-to-event efficacy endpoints will take place when all patients have completed a minimum of three years follow-up.

All patients registered on the study will be accounted for in reports of study outcomes. Descriptive statistics of characteristics measured at baseline for all patients registered will be reported: as number of patients, median, minimum and maximum for continuous variables, and as counts and percentages for categorical variables.

In order to address the primary objective of feasibility, the proportion of patients consenting to undergo the combined regimen of radiotherapy and chemotherapy once invited to participate in the study and the proportion of patients completing protocol treatment will be calculated with accompanying two-sided 95% confidence intervals based on exact values of the binomial distribution.

For time-to-event endpoints a study close-out date will be determined at the time of analysis in order to minimise bias in the reporting of time to failure and survival outcomes. This will generally be taken to be the earliest of the dates of last contact of the patients who are still alive and being followed up. Thus, with the exception of any patients who have been lost to follow-up, the status of all patients in the study should be known at this date.

The efficacy endpoints of time to local recurrence, time to loco-regional recurrence, time to distant recurrence, failure-free survival and overall survival will be estimated using the Kaplan-Meier product limit method; annual recurrence and survival rates will be calculated along with 95% confidence intervals. Exploratory analyses investigating associations between patient characteristics and efficacy endpoints will also be performed using Cox proportional hazards regression.

The incidence and worst grade of toxicities/adverse events will be summarised in detail using descriptive statistics.

Biological Sub-study

Consent will be sought from participants for future use of their tumour tissue for biological sub-studies including analysis of SPARC expression. SPARC expression has been shown to predict response to taxane therapy in breast cancer. Understanding the utility of these potential biomarkers in carcinosarcoma of the uterus may allow more tailored management of this disease in future. Ability for the sub-study to proceed will be contingent on additional funding being obtained.