A randomized phase III study of neoadjuvant chemotherapy followed by surgery versus surgery alone for patients with High Risk RetroPeritoneal Sarcoma

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This study has been transitioned to CTIS with ID 2023-505261-84-00 check the CTIS register for the current data. The primary objective of this study is to assess whether preoperative chemotherapy, as an adjunct to curative-intent surgery, improves...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Soft tissue neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52562

Source
ToetsingOnline

Brief title
STRASS 2

Condition

- Soft tissue neoplasms malignant and unspecified
- Soft tissue therapeutic procedures

Synonym
retroperitoneal sarcoma, sarcoma

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: EORTC;Anticancer Fund

Intervention

Keyword: High risk retroperitoneal sarcoma, Preoperative chemotherapy, Surgery

Outcome measures

Primary outcome

Disease free survival (which includes as events: distant progression on

neoadjuvant treatment, local progression if not followed by R0/R1 surgery,

non-operable tumours, local recurrence and/or distant metastases, R2 and death)

Secondary outcome

• Overall survival

• Recurrence free survival

• Distant metastases free survival

• Cumulative incidence of local recurrences

• Cumulative incidence of distant metastases

• Radiological response to neoadjuvant chemotherapy according to RECIST

• Radiological response to neoadjuvant chemotherapy according to CHOI

• Pathological response

• Safety and toxicity of neoadjuvant chemotherapy

• Perioperative complications

• Late complications

• Health-Related Quality of life (EORTC QLQ-C30 + Item list from QLQ-STO22)

Study description

Background summary

High grade dedifferentiated liposarcoma (LPS) and leiomyosarcoma (LMS) originating from the retroperitoneum have a dismal prognosis, with a risk of death in excess of 70% at 5 yrs. While WDLPS and G1-G2 DDLPS, the 2 most common histological subtypes originating at this site, predominantly fail locally, it has become evident over the past years that high grade DDLPS and LMS are characterized by a high metastatic risk, which is the leading cause of death. Systemic chemotherapy has the potential to address the metastatic risk and improve relapse free survival as well as overall survival. The neoadjuvant setting is preferable for a study in this disease, as it allows to assess drug activity as well as efficacy, study tumour biology and response to therapy, and immediately address the systemic risk which is the cause of death of these patients. In addition, patients will have to undergo a major abdominal procedure with a high chance to lose one kidney en bloc with the tumour. It's therefore easier to perform chemotherapy in the preoperative phase, when patients have not yet undergone the procedure above.
An attempt to formally study the possible benefit of chemotherapy in these high risk histologic subtypes has not previously been performed.

Study objective

This study has been transitioned to CTIS with ID 2023-505261-84-00 check the CTIS register for the current data.

The primary objective of this study is to assess whether preoperative chemotherapy, as an adjunct to curative-intent surgery, improves the prognosis of patients with high risk de-differentiated liposarcoma (DDLPS) and leiomyosarcoma (LMS) as measured by disease-free survival.

Secondary objectives:
• To assess whether there is a difference in the overall survival, recurrence free survival, distant metastases free survival, cumulative incidence of local recurrences and cumulative incidence of distant metastases between patients undergoing curative-intent surgery alone and those undergoing preoperative chemotherapy followed by curative intent surgery
• To assess tumour response in patients undergoing preoperative chemotherapy
• To assess the toxicity profile of preoperative chemotherapy given as "neoadjuvant" treatment to curative intent surgery in patients with high risk retroperitoneal (RPS) and of surgery alone
• To assess whether there is a difference in quality of life between patients undergoing curative-intent surgery alone and those undergoing preoperative

chemotherapy followed by curative intent surgery

Study design

This is a randomized, multicentre, open-label phase III trial of neoadjuvant chemotherapy followed by surgery versus surgery alone in patients with RPS. The randomization will be stratified by institution and histology: liposarcoma LPS or leyomiosarcoma (LMS).
Patients will be randomized to either Standard arm: large en-bloc curative intent surgery or Experimental arm: 3 cycles of neoadjuvant chemotherapy followed by curative intent surgery
The primary endpoint of the study is disease free survival which includes as events: distant progression on neoadjuvant treatment, local progression if not followed by R0/R1 surgery, non-operable tumours, local recurrence and/or distant metastases, R2 and death.

Intervention

As part of the study, half of the patients receive chemotherapy pre-treatment, which consists of three doses that are administered clinically. This means 3 times admission to the hospital for 3-5 days once every 3 weeks, a total of more than 2 months. The other half of the patients receive surgery alone. Please note that the current standard of care is often neoadjuvant chemotherapy as well, but that now depends on certain patient factors. In this study we randomize patients between chemotherapy and surgery alone, so in the end the load for the whole group is comparable to the load in the standard of care in the current practice.

Study burden and risks

The psychological burden caused by taking part of the clinical trial and also the possibility of more toxicity because of the chemotherapy.

Contacts

Public
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E. Mounier 83/11
Brussel 1200
BE
Scientific
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E. Mounier 83/11
Brussel 1200
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Histologically proven primary high risk leiomyosarcoma (LMS) or Liposarcoma (LPS) of retroperitoneal space or infra-peritoneal spaces of pelvis.
- LMS: Any grade and size > 5 cm
- LPS (diagnosis based on MDM2 and CDK4 expression on IHC; additional proof of MDM2 amplification is highly recommended but not mandatory):
* Grade 3 DDLPS OR
* Confirmed grade 2 DDLPS on biopsy only if:
FNCLCC score = 5 and clear necrosis on imaging whether or not present on the biopsy OR
* High risk gene profile as determined by the Complexity INdex in SARComas (CINSARC-high)
• Unifocal tumour
• Resectable tumour: resectability is based on pre-operative imaging performed within 28 days before randomization (CT-abdomen, potentially also with MRI) and has to be defined by the local treating sarcoma team. A patient is not considered resectable when the expectation is that only an R2 resection is feasible.
Criteria for non-resectability are:
- Involvement of the superior mesenteric artery, aorta, coeliac trunk and/or portal vein
- Involvement of bone
- Growth into the spinal canal

- Progression of retro-hepatic inferior vena cava leimyosarcoma towards the right atrium
- Infiltration of multiple major organs like liver, pancreas and or major vessels
• Patient must have radiologically measurable disease (RECIST 1.1), as confirmed by imaging within the 28 days prior to randomization. CT thorax abdomen pelvis with IV contrast is the preferred imaging modality. In case of any contra-indications (medical or regulatory), it is allowed to perform a non-contrast CT thorax + MRI abdomen & pelvis.
• Collection of tumor tissue and blood samples for central pathology review and translational research are mandatory. If tumor tissue is not available and/or patient does not consent, patient will not be eligible for this trial.
• >= 18 years old (no upper age limit)
• WHO performance status <= 2
• Adequate haematological and organ function assessed within 21 days prior to randomization
• American Society of Anesthesiologist (ASA) score < 3
• Women of child bearing potential (WOCBP) must have a negative serum pregnancy test within 3 days prior to randomization.
• WOCBP in both arms should use higly effective birth control measures, during the study treatment period and for at least 6 months after the last dose of chemotherapy or date of surgery (except for women receiving chemotherapy with ifosfamide who should continue contraception until 1 year after last day of treatment). A highly effective method of birth control is defined as a method which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.
• For men in the experimental arm: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm
• Female subjects who are breast feeding should discontinue nursing prior to the first day of study treatment and until 6 months after the last study treatment.
• Before patient randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.

Exclusion criteria

• Sarcoma originating from bone structure, abdominal or gynecological viscera
• Extension through the sciatic notch or across the diaphragm
• Metastatic disease
• Any previous surgery (excluding diagnostic biopsy), radiotherapy

or systemic therapy for the present tumour
• Hypersensitivity to doxorubicin, ifosfamide, dacarbazine or to any of their metabolites or to any of their excipients
• Congestive heart failure
• Angina pectoris
• Myocardial infarction within 1 year before randomization
• Uncontrolled arterial hypertension defined as blood pressure >= 150/100 mm Hg despite optimal medical therapy
• Uncontrolled cardiac arrhythmia
• Previous treatment with maximum cumulative doses (450mg/m² Doxorubicin or equivalent 900mg/m² Epirubicin) of doxorubicin, daunorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones
• Active and uncontrolled infections
• Vaccination with live vaccines within 30 days prior to study entry
• Inflammation of the urinary bladder (interstitial cystitis) and/or obstructions of the urine flow.
• Other invasive malignancy within 5 years, with the exception of adequately treated non-melanoma skin cancer, localized cervical cancer, localized and Gleason <= 6 prostate cancer.
• Uncontrolled severe illness, infection,medical condition (including uncontrolled diabetes), other than the primary LPS or LMS of the retroperitoneum.
• Female patients who are pregnant or breastfeeding or female and male patients of reproductive potential who are not willing to employ effective birth control method.
• Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before randomization in the trial
• Known contraindication to imaging tracer and to MRI

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-02-2022
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dacarbazin
Generic name:	Dacarbazin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Doxorubicin
Generic name:	Doxorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Epirubicin
Generic name:	Epirubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Holoxan
Generic name:	Ifosfamide
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	23-09-2020
Application type:	First submission
Review commission:	METC NedMec

Approved WMO Date:	09-07-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-12-2022
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-505261-84-00

Register	ID
EudraCT	EUCTR2019-003543-30-NL
ClinicalTrials.gov	NCT04031677
CCMO	NL73078.031.20