TOLERANCE: a 3 arm randomized study on healTh-related quality Of Life of ElderRly pAtients with advaNced soft tissue sarComa undergoing doxorubicin every three weeks or doxorubicin weekly or cyclophosphamide plus predniso(lo)ne treatment

Published: 11-07-2022
Last updated: 06-04-2024

Main objectiveThe primary objective of this study is to assess whether a higher HRQoL, in terms of impact of the disease and its treatment on physical and role functioning, is achieved with metronomic schedules of doxorubicin or cyclophosphamide…

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

Summary

ID

NL-OMON51478

Source
ToetsingOnline

Brief title
TOLERANCE

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
Soft tissue tumor; cancer

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; Rising Tide Foundation and Fonds Cancer (FOCA)

Intervention

Keyword: Advance soft tissue sarcoma, Doxorubicin, Quality of life, Randomized

Outcome measures

Primary outcome

Primary endpoint:

• Difference in physical and role functioning at 12 weeks.

Physical functioning (PF) is one of the functional scale scores of the EORTC QLQ-C30 questionnaire. The scale score is based on the mean score of 5 items measuring patients' self-reported ability to perform physical activities. The scale score can range from 0-100 with higher scores indicating better functioning.

Role functioning (RF) is one of the other functional scale scores of the EORTC QLQ-C30 questionnaire. The scale score is based on the mean score of 2 items measuring patients' self-reported ability to perform daily tasks related to household, work or recreation. The scale score can range from 0-100 with higher scores indicating better functioning.

Secondary outcome

Secondary endpoints:

• Difference in all other EORTC QLQ-C30 scales at 12 weeks

• Sensitivity: Difference in physical and role functioning at 24 weeks

• Difference in progression free survival (PFS) at 12 weeks according to the

RECIST 1.1

• Efficacy: PFS, overall survival (OS), tumour response (RECIST 1.1)

• Safety: Adverse Events (AEs) according to CTCAE v5.0

• Tolerability: treatment discontinuation, delay and/or reduction.

Exploratory endpoints:

• Difference in ELD14 scales

• Difference in ADL scales

Study description

Background summary

Elderly patients 65 years or older with advanced STS are largely underrepresented in clinical trials of first-line chemotherapy. Elderly patients participating in clinical trials often have an excellent performance status, which is not representative of an unselected *real-life* elderly STS population. Therefore, treatment decisions in routine clinical practice are hampered by the limited scientific evidence on the efficacy and toxicity of doxorubicin and other chemotherapy regimes in elderly patients with advanced STS. These findings provide rationale for the development of novel trials for elderly patients taking into account patient-reported daily functioning and incorporating GA as a measure of physiologic age.

Study objective

Main objective
The primary objective of this study is to assess whether a higher HRQoL, in terms of impact of the disease and its treatment on physical and role functioning, is achieved with metronomic schedules of doxorubicin or cyclophosphamide plus predniso(lo)ne versus the standard doxorubicin treatment.
Secondary objectives:
• To assess whether there is an improvement in quality of life, in terms of

impact of the disease and its treatment on social, emotional and cognitive functioning as well as self-reported symptoms and overall quality of life/health perception, among patients treated with metronomic doxorubicin, patients treated with metronomic cyclophosphamide plus predniso(lo)ne and patients treated with standard doxorubicin regimen.
• To assess whether there is a difference in the progression free survival, overall survival and tumour response among patients treated with metronomic doxorubicin, patients treated with metronomic cyclophosphamide plus predniso(lo)ne and patients treated with standard doxorubicin regimen.
• To assess the toxicity profile of the three treatment arms
• To assess the tolerability of the three treatment arms
Exploratory objectives:
• To assess whether there is a difference in quality of life, in terms of EORTC QLQ-ELD14 scales, among patients treated with metronomic doxorubicin, patients treated with metronomic cyclophosphamide plus predniso(lo)ne and patients treated with standard doxorubicin regimen.
• To assess whether there is a difference in maintaining fundamental skills that are required to care for oneself, as measured by the ADL (Activities of Daily Living) tool, among patients treated with metronomic doxorubicin, patients treated with metronomic cyclophosphamide plus predniso(lo)ne and patients treated with standard doxorubicin regimen.

Study design

This is a multi-centre, open label, randomized phase 3 study (1:2:2 randomization). After confirmation of the eligibility criteria, 185 patients will be randomized 1:2:2 to either the control arm (doxorubicin 60-75 mg/m² IV every 3 weeks) or experimental arm 1 (doxorubicin 12 mg/m2 IV every week) or experimental arm 2 [cyclophosphamide tablets 100 mg twice a day (morning and evening) plus prednisolone/prednisone tablets 10 or 20 mg once a day (in the morning), on day 1 to day 7 of each 14 day cycle]. HRQoL assessment will be performed every 3 weeks during the first 12 weeks and every 12 weeks thereafter until 1 year after start of treatment. Disease evaluation will be performed every 12 weeks until progression.

Intervention

Experimental arm 1
Patients randomized to the experimental arm 1 will be treated with doxorubicin 12 mg/m2 administered weekly intravenously (bolus or short infusion as per local standard practice) for a maximum of 450 mg/m2 until disease progression, unacceptable toxicity, patient*s refusal or occurrence of concomitant disease requiring intervention that interferes with the study treatment, whichever comes first. Adequate antiemetic treatment, supportive measures and hematopoietic growth factors should be delivered according to local treatment standards.

Experimental arm 2
Patients randomized to the experimental arm 2 will be treated with oral cyclophosphamide 100 mg BD (at approximately 8:00 and 19:00) plus prednisolone/prednisone 10 or 20 mg daily (in the morning) on day 1 to day 7 of each 14-day cycle until disease progression, unacceptable toxicity, patient*s refusal or occurrence of concomitant disease requiring intervention that interferes with the study treatment, whichever comes first.
Use of haematopoiesis stimulating agents (colony-stimulating factors and erythropoiesis stimulating agents) may be considered to reduce the risk of myelosuppressive complications and/or help facilitate the delivery of the intended dosing.
Adequate amount of fluids (1.5 L- 2 L) should be ingested daily (or infused) to force diuresis in order to reduce the risk of urinary tract toxicity.

Study burden and risks

- Possible side effects of chemotherapy treatment.
- Regular visits at the hospital including physical examinations, blood withdrawal, Quality of Life questionnaires, biopsies (if archived material is not available) and CT scans.

Contacts

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

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

Avenue E. Mounierlaan 83/11
Brussel 1200
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Elderly (65 years and older)

Inclusion criteria

• Histologically proven advanced unresectable or metastatic soft tissue sarcoma (STS)
• Representative formalin fixed, paraffin embedded tumor blocks or slides, either from the primary tumor or a metastatic lesion, must be available for central review.
• Age >= 65 years of age (patients between 65 and 69 years old are eligible if G8 score <= 14; patients >= 70 years old are eligible independent of G8 score)
• WHO performance status 0 - 2
• Life expectancy based on other significant morbidity of >= 6 months
• Presence of measurable disease (according to RECIST 1.1), as confirmed by imaging within the 28 days prior to randomization. CT 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 + MRI.
• Progressive disease at entry based on RECIST 1.1
• Patients amenable to receive doxorubicin according to investigator's assessment
• Adequate haematological and organ function assessed prior to randomization (protocol version 2.0; pages 22-23, section 4.1)
• Completion of EORTC QLQ-C30 and EORTC QLQ-ELD14.
• Assessment of G8 geriatric screening tool
• For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined in protocol version 2.0; pages 22-23; section 4.1)
• Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations including commitment to completing questionnaires during the course of the study.

Exclusion criteria

• Gastrointestinal stromal tumors (GISTs)
• Symptomatic or known brain metastasis
• Any prior treatment with anthracyclines
• Any prior systemic treatment for metastatic STS
• Any prior, current or planned treatment with radiotherapy of head and neck, thorax or liver
• Inability to swallow and/ or retain oral tablets

• Rare hereditary galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption
• Hypersensitivity to doxorubicin, cyclophosphamide, prednisolone, prednisone or to any of their metabolites or to any of their excipients
• Uncontrolled severe illness, including but not limited to:
- Congestive heart failure
- Angina pectoris
- Acute inflammatory heart disease
- Myocardial infarction within 1 year before randomization
- Arterial hypertension defined as blood pressure >= 150/100 mm Hg despite optimal medical therapy
- Uncontrolled cardiac arrhythmia
- Increased haemorragic tendency
- Severe osteoporosis
- Peptic ulcer
- Uncontrolled diabetes
- Bone marrow aplasia
- Psychosis
- Active or uncontrolled infections among which those requiring systemic antibiotics or antimicrobial therapy.
- Inflammation of the urinary bladder (interstitial cystitis) and/or obstructions of the urine flow.
• Vaccination with live vaccines within 30 days prior to study entry
• Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment.
• Known contraindication to MRI
• Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and its active requirements (including completion of questionnaires) and follow-up schedule; those conditions should be discussed with the patient before randomization in the trial

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:	Recruitment stopped
Start date (anticipated):	12-12-2022
Enrollment:	38
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cyclophosphamide
Generic name:	Cyclophosphamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Doxorubicin
Generic name:	Doxorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prednisolone
Generic name:	Prednisolone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prednisone
Generic name:	Prednisone
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	11-07-2022
Application type:	First submission
Review commission:	METC NedMec

Approved WMO Date:	22-09-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-12-2022
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
EudraCT	EUCTR2021-000125-27-NL
ClinicalTrials.gov	NCT04780464
CCMO	NL81448.041.22