Neoadjuvant trial on the efficacy of propranolol monotherapy in angiosarcoma.

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The primary objective is to determine the clinical response of propranolol monotherapy in patients with angiosarcoma. The secondary endpoint is to assess the pathologic response of propranolol monotherapy in patients with angiosarcoma.

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

Summary

ID

NL-OMON49514

Source
ToetsingOnline

Brief title
propranolol in angiosarcoma

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
angiosarcoma, soft tissue cancer arising from the blood vessels

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Anticancer Fund Belgium

Intervention

Keyword: angiosarcoma, neoadjuvant, propranolol

Outcome measures

Primary outcome

The primary endpoint is the clinical response according to RECIST criteria. If propranolol leads to a response in >=3 out of 14 patients, this treatment modality is highly interesting and should be tested further in a randomized trial. A response is defined as SD, PR or CR with improvement in clinical characterstics.

Secondary outcome

The secondary endpoint is the histologic response defined as a decrease of >30% of Ki-67 index between pre- and post-propranolol treatment biopsies.

Study description

Background summary

Propranolol hydrochloride, a β-blocker, has recently been repurposed against a benign vascular tumor called hemangioma with 88% complete or near complete resolution of the treated lesions. Also, several small case reports/series have suggested that propranolol could be repurposed to treat locally advanced or malignant vascular tumor, angiosarcoma. These patients with locally advanced or metastatic angiosarcoma were treated with propranolol, in combination with various chemotherapy regimens, including combination therapy with cyclophosphamide and vinblastine based chemotherapy. Preclinical studies have demonstrated synergy between propranolol in combination with vinblastine in in vitro angiosarcoma models. A reduction in proliferation index of angiosarcoma has also been reported in response to propranolol monotherapy in one patient. In terms of safety in cancer patients, propranolol has been or is being used in more than 20 clinical oncology trials, including one clinical trial in advanced angiosarcoma in combination with cyclophosphamide (NCT02732678) with no major safety concerns when cardiovascular monitoring is performed (i.e. dose adapted to blood pressure and heart rate).

Since there is few data available regarding the activity and mechanism of action of propranolol as a single agent for angiosarcoma, both in the primary and metastatic setting, our goal is to evaluate the activity in a window study in cutaneous angiosarcoma patients in a neoadjuvant setting before they proceed with the standard anti-cancer treatment.
The goal of this neoadjuvant window of opportunity study is therefore to prospectively evaluate the activity of propranolol in the clinical setting as monotherapy, where the neoadjuvant setting provides a good opportunity to rapidly evaluate both the clinical response and pathological response, without a significant delay in anti-cancer treatment.

Study objective

The primary objective is to determine the clinical response of propranolol monotherapy in patients with angiosarcoma. The secondary endpoint is to assess the pathologic response of propranolol monotherapy in patients with angiosarcoma.

Study design

Design: Single arm neoadjuvant window of opportunity phase II study to explore the activity of propranolol monotherapy in angiosarcoma.
Treatment: Propranolol monotherapy 40-80 mg BID or TID if tolerated.
Treatment plan*:
Dose escalation of propranolol before standard anti-cancer treatment
Propranolol (tablet, 40 mg)
Day 1 - Day 7 1 x 40 mg, 2x/day
Day 8 - Day 14 2 x 40 mg, 2x/day
Day 15 - Day of surgery or biopsy 2 x 40 mg, 3x/day

Tapering of propranolol post- surgery/biopsy Propranolol (tablet, 40 mg)
Day 1 post-surgery/biopsy - Day 7 post-surgery/biopsy 2 x 40 mg, 2x/day
Day 8 post-surgery/biopsy - Day 14 post-surgery/biopsy 1 x 40 mg, 2x/day
*Propranolol will be increased to the next dose level if heart rate is >60, systolic blood pressure (BP) is >110 and previous dose is well tolerated.
In case of hypotension (BP < 90/60 mmHg) or bradycardia (heart rate < 55bpm), or symptoms of bradycardia or hypotension (dizziness, syncope) the dose will be reduced to the previous level. In case of serious bradycardia (heart rate < 50bpm) the treatment will be put on hold until an acceptable heart rate > 55 bpm is reached, at which point the dose of the previous level will be administered.

Duration/schedule: When patients are diagnosed, standard anti-cancer treatment must be scheduled within 6 weeks. Since propranolol treatment can start immediately after the diagnosis and will be continued until the day the patient starts with the standard anti-cancer treatment, this is a so-called window of

opportunity study. The duration of study treatment will be 3-6 weeks.

Intervention

3-6 weeks treatment with propranolol according to the treatment plan as stated in "study design".

Study burden and risks

Patients will be evaluated on the outpatient clinic on a weekly basis with only minimal blood draws for safety assessments. Additional burden consist of extra visits (3-6) including blood draws and physical examination, a dairy for study medication needs to be filled in, extra biopsy or radiologic assessments will be done if applicable. The patients are treated with propranolol with a well-known safety profile.

Contacts

Public
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL
Scientific
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

oHistological proof of angiosarcoma
oPatients with primary, recurrent and metastasised disease are eligible;
oPatients with a window of at least 3 weeks before surgery or systemic therapy
oAge of 18 years or more;
oAble and willing to give written informed consent;
oWHO performance status of 0, 1 or 2;
oEvaluable disease according to RECIST 1.1 criteria; radiologic visible disease is not obligated in patients with cutaneous angiosarcoma
oAt least one tumor lesion accessible to safely biopsy per clinical judgement of the treating physician

Exclusion criteria

o Contraindication for propranolol therapy,
o Current treatment with β-blockade therapy.
o Any anticancer treatment within 30 days prior to receiving the first dose of investigational treatment; with the exception of hormonal therapy for breast cancer.
o Concurrent treatment with an anticancer therapy: with the exception of hormonal therapy for breast cancer.
o Pregnancy.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	17-03-2020
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	inderal
Generic name:	propranolol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-10-2019
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-11-2019
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-11-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	04-11-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 23603
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2019-002947-41-NL
CCMO	NL71090.031.19
OMON	NL-OMON23603