Neoadjuvant propranolol in angiosarcoma patients

No registrations found.

Ethical review	Not applicable
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23603

Source
Nationaal Trial Register

Brief title
PropAngio

Health condition

Angiosarcoma

Sponsors and support

Primary sponsor: The Netherlands Cancer Institute Antoni van Leeuwenhoek ziekenhuis
Source(s) of monetary or material Support: Anticancer Fund

Intervention

Outcome measures

Primary outcome

The primary endpoint is the clinical response according to RECIST 1.1 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. 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 CR, PR, or SD with an

improvement in clinical characteristics, like thickness, erythema, necrosis or edema of the inflicted area.

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

Rationale:
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 metastatic angiosarcoma. These patients were treated with propranolol, in combination with various chemotherapy regimens, such as cyclophosphamide and vinblastine. 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 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 histological response, without a significant delay in anti-cancer treatment.

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

Study 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.

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.

Study objective

To determine the clinical and histologic response of propranolol monotherapy in patients with angiosarcoma.

Study design

The primary and secondary endpoints will be determined after 3-6 weeks of study treatment.

Intervention

propranolol monotherapy

Contacts

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Eligibility criteria

Inclusion criteria

o Histological proof of angiosarcoma
o Patients with primary, recurrent and metastasised disease are eligible;
o Patients with a window of at least 3 weeks before surgery or systemic therapy;
o Age ≥18 years;
o Able and willing to give written informed consent;
o WHO performance status of 0, 1 or 2;
o Evaluable disease according to RECIST 1.1 criteria; radiologic visible disease is not obligated
o Minimal acceptable safety laboratory values
o ANC of ≥ 1.5 x 109 /L
o Platelet count of ≥ 100 x 109 /L
o Hepatic function as defined by serum bilirubin ≤ 1.5 x ULN, ASAT and ALAT ≤ 2.5 x ULN
o Renal function as defined by serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 50 mL/min (by Cockcroft-Gault formula);
o At least one tumor lesion accessible to safely biopsy per clinical judgement of the treating physician

Exclusion criteria

o Contraindication for propranolol therapy, like severe hypotension or bradycardia, sick-sinus syndrome, second or third grade heart block, cardiogenic shock, untreated heart failure, severe peripheral vascular disease asthma or other obstructive lung diseases, untreated pheochromocytoma, metabolic acidosis, prolonged fasting.
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 Patients with known alcoholism, drug addiction and/or psychiatric of physiological condition which in the opinion of the investigator would impair study compliance;
o Evidence of any other disease, neurological or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment-related complications;
o Pregnancy;

o Legal incapacity.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	25-10-2019
Enrollment:	14
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Yes

Plan description
All essential documents (including patient files, the Investigator Study File, CRFs and electronic study data), data management and statistical files will be kept for 15 years. Results of the study will be published in an international journal, independently of the results.

Ethics review

Not applicable

Application type:	Not applicable

Study registrations

Followed up by the following (possibly more current) registration

ID: 49514
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL8118
CCMO	NL71090.031.19
OMON	NL-OMON49514

Study results