Phase II study of oral metformin for intravesical treatment of non- muscle-invasive bladder cancer (TROJAN)

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON25176

Source
NTR

Brief title
TROJAN

Health condition

Non-muscle-invasive bladder cancer

NMIBC

Bladder cancer

Blaaskanker, niet-spierinvasief blaascarcinoom

Sponsors and support

Primary sponsor: Amsterdam UMC, AMC
Source(s) of monetary or material Support: ZonMW project 848082004

Intervention

Outcome measures

Primary outcome

Overall response: The primary outcome is the objective response rate (complete responses) after 3 months of treatment with metformin. Evaluable patients are those who have received at least 500 mg metformin twice daily for one week and who undergo a cystoscopy for marker lesion removal.

Secondary outcome

Time to recurrence: The duration of the time to recurrence of NMIBC after stopping metformin treatment. Patients will be followed for a maximum duration of 5 years.

Toxicity: The number of grade 1-4 and grade 5 (fatal) NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE) events during treatment with metformin. All patients will be evaluable for toxicity from the time of their first treatment with metformin.

Partial response: At least 30% reduction in the longest diameter of the marker lesion.

Patient reported outcomes: using SF-36 and EORTC QLQ-NMIBC24 questionnaires; before metformin treatment, after 6 weeks and after 3 months.

Study description

Background summary

A multi-center, open-label, phase II clinical study of metformin in up to 49 patients with low-grade NMIBC with the aim to determine the overall response to administration of oral metformin for 3 months in a marker tumour deliberately left following transurethral resection of multiple, papillary NMIBC tumours. All patients will receive metformin orally at doses up to 1500 mg twice daily. Metformin treatment will start within 2 weeks following transurethral resection, in which all but the marker lesion will be resected. After 3 months of metformin treatment, the effect of metformin on the marker lesion is evaluated by cystoscopy and biopsy under anaesthesia. Residual tumour, if present at this evaluation, will be resected. In case of complete disappearance of the marker lesion the former tumour area will be biopsied.

Study objective

Metformin has antineoplastic activity but thus far has not shown clinical benefit in the treatment of cancer in humans.
Metformin is excreted by the kidneys and accumulates unchanged in the urine where, compared to serum, it reaches a 240-fold higher concentration in urine of mice resulting in improved survival in mice with bladder cancer.

In humans, NMIBC could be exposed to efficacious metformin concentrations because metformin reaches a 100-fold higher concentration in urine compared to serum.

Study design

Overall response: 3 months

Time to recurrence: 5 years

Toxicity: 3 months

Partial response: 3 months

Patient reported outcomes: t=0 weeks, 6 weeks and 3 months

Intervention

TURB leaving a single marker lesion followed by oral metformin treatment.

Contacts

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Eligibility criteria

Inclusion criteria

-Age > 18 years.

-Patients with primary or recurrent multiple histologically confirmed Ta or T1 (non-muscle invasive), G1 or G2 (low grade) urothelial carcinoma of the bladder with no evidence of carcinoma in situ.

-Patients must have at least 2 lesions but no more than 10.

-The resected lesions must contain detrusor muscle to confirm a Ta/T1 disease.

-All visible lesions must be completely removed by transurethral resection at entry to the study, except for an untouched marker lesion measuring 0.5-1.0 cm in its greatest dimension.

-Bimanual examination immediately following transurethral resection under anaesthesia should be carried out and no mass should be felt.

-Adequate renal function (creatinine <150 µmol/L and/or an eGFR >60 ml/L).

-Adequate liver function (bilirubin <1.5 times upper limit of normal, ALAT or ASAT <2.5 the upper limit of normal).

-Eligible patients must be fully informed of the investigational nature of the study and written signed informed consent must be obtained prior to any study specific investigations.

-Mentally, physically, and geographically able to undergo treatment and follow up.

Exclusion criteria

-Patients having muscle-invasive disease (stage T2 or greater) or CIS.

-Patients with grade 3 (high-grade) tumours.

-Patients with diabetes mellitus receiving metformin or having received metformin in the past 6 months.

-Patients who have received intravesical treatment (chemotherapy or immunotherapy) within the last 3 months.

-Patients that are currently receiving other anti-cancer therapy.

-Patients with existing urinary tract infection or recurrent severe bacterial cystitis.

-Patients that need to be treated with a transurethral catheter.

-Patients with urogenital tumours with histology other than urothelial carcinoma (i.e. squamous cell or adenocarcinoma) or with urothelial carcinoma involving the upper tract or the prostatic urethra.

-Patients with a history of other primary malignancy (other than squamous or basal cell skin cancers or cone biopsied CIS of the uterine cervix or prostate carcinoma treated curatively with normal PSA values at inclusion) in the last five years.

-Patients with active, uncontrolled impairment of the renal, hepatobiliary, cardiovascular,

gastrointestinal, urogenital, neurologic or hematopoietic systems that, in the opinion of the investigator, would predispose to the development of complications from the administration of metformin.

-Patients who are using loop diuretics, cimetidine, ranitidine, cetirizine, trimethoprim, vandetanib, kinidine and/or HIV medication, for which no reasonable alternative is available.

-Women who are pregnant or lactating. Individuals of reproductive potential may not participate unless agreeing to use an effective contraceptive method for themselves and/or their sexual partner.

-Patients with ECOG-WHO performance status of 3 or 4.

-Patients with a known history of alcohol abuse.

-Patients with a known hypersensitivity to metformin.

-Patients who in the investigator's opinion, cannot comply with provisions of the protocol or do not understand the nature of the study.

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):	12-02-2019
Enrollment:	49
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Ethics review

Positive opinion

Date:	08-02-2019
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 56329
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL7496
CCMO	NL62588.018.17
OMON	NL-OMON56329

Study results