Trained immunity induced by BCG in urothelial carcinoma

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON47732

Source
ToetsingOnline

Brief title
Tribute

Condition

- Renal and urinary tract neoplasms malignant and unspecified
- Bladder and bladder neck disorders (excl calculi)

Synonym
Non-muscle invasive bladder cancer

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: BCG, bladder cancer, immunotherapy, trained immunity

Outcome measures

Primary outcome

Study parameters include (i) histone 3 lysine 4 (H3K4) trimethylation (me3), H3K9me3, and H3K27 acetylation levels at the TNF-*, IL-6 and IL1-b promoters in circulating monocytes during BCG treatment; (ii) TNF-*, IL-6 and IL-1b levels produced by ex vivo stimulated monocytes during treatment, (iii) DNA variant genotypes and molecular bladder tumor subtypes, (iv) CyPRIT score, (v) (time to) tumor recurrence.

Secondary outcome

NA

Study description

Background summary

Intravesical Bacillus Calmette-Guérin (BCG) therapy is considered standard treatment in high-risk non-muscle invasive bladder cancer (NMIBC) to prevent tumor recurrence and maybe even progression. The treatment protocol entails an induction cycle of 6 weekly bladder instillations and a number of maintenance cycles in the 1-3 years thereafter. The immune system is thought to play an important role in the response to BCG but the exact working mechanism is unknown. Also, it is not yet possible to identify patients who do (not) benefit from BCG. Recently, it was shown in vitro and ex vivo that response to BCG is mediated by epigenetic reprogramming of innate immune cells (*trained immunity*) and that response to BCG may be predicted via a urinary cytokine panel (CyPRIT).

Study objective

This study has 4 objectives: to (1) describe the trained immunity response that is triggered by intravesical BCG therapy in high-risk NMIBC patients; (2)

compare the trained immune response between patients with and without tumor recurrence within 1 year after BCG therapy start; (3) explore the association between common germline DNA variants and molecular tumor subtypes and the trained immunity response; (4) replicate the reported predictive value of the CyPRIT score for BCG response (1-year recurrence).

Study design

This is a multi-centre, observational cohort study with at least 1 year follow-up for included patients (there is no treatment intervention; treatment is according usual clinical practice).

Study burden and risks

The burden and risks associated with participation in the study are considered acceptable. The number of hospital visits is equal to what patients with these criteria is offered when they are not participating in this study. Extra in this study are the collection of (1) urine samples prior to the 1st and prior to and 4 to 8 hours after the 6th BCG induction instillation and prior to and after the last instillation in the first maintenance cycle (5 urine samples); (2) blood samples prior to the 1st and after the 2nd and 6th BCG instillation of the induction cycle and prior to the 1st and after the 3rd instillation of 3 maintenance cycles (9 blood samples). Participation has no direct benefit for patients.
This study can only be performed in patients with non-muscle invasive bladder cancer and that receive BCG installation therapy for the treatment of this disease.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Presence of high-grade Ta or T1 urothelial carcinoma of the bladder with or without carcinoma in situ; tumor can be primary or recurrent
2. Able to communicate in Dutch, and read and understand the patient information and informed consent form and fill out questionnaires
3. Signed and dated informed consent form
4. Complete resection of (visible) tumor at start of BCG therapy as determined via re-TURT or negative cystoscopy/cytology (at most 6 weeks prior to BCG therapy initiation)

Exclusion criteria

1. Any previous intravesical BCG therapy
2. Presence of primary CIS only
3. Presence of histopathologically proven muscle-invasive urothelial carcinoma of the bladder at first or re-TUR surgical specimens
4. Presence of tumor stage cN1 of cM1 as assessed by CT-thorax/abdomen
5. Presence of any upper urinary tract tumors
6. Histology subtype of resected tumor is not predominant urothelial carcinoma
7. Presence of another malignancy other than basal cell carcinoma of the skin or prostate cancer under active surveillance
8. Presence of pregnancy or lactation
9. Presence of active tuberculosis, any form of immunodeficiency (e.g. HIV + serology, transplant recipients) and/or any other contraindication of BCG therapy
10. Patients who have received any systemic cytostatic agents within the last 3 months
11. Patients younger than 18 and older than 85 years of age
12. Patients with uncontrollable urinary tract infection

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-06-2018
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	13-06-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-10-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-06-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-06-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	26-09-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
CCMO	NL60341.091.17