Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial.

Published: 30-09-2014
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The primary objective of this study is to identify if reduced number of BCG instillations are not inferior to standard number and dose intravesical BCG treatment in patients with high grade NMIBC. The primary endpoint for inferiority analysis is...

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

Summary

ID

NL-OMON45214

Source
ToetsingOnline

Brief title
NIMBUS

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder, malignant bladder cancer

Research involving
Human

Sponsors and support

Primary sponsor: European Association of Urology
Source(s) of monetary or material Support: EAU Research Foundation

Intervention

Keyword: Bacillus Calmette-Guérin, Efficacy and safety, Intravesical instillation, Non-Muscle Invasive Bladder Cancer

Outcome measures

Primary outcome

Primary endpoint is the time to first recurrence.

Secondary outcome

Secondary endpoints:

- number and grade of recurrent tumors

- rate of progression to a higher stage (T2 or higher)

- incidence and severity of side effects.

Study description

Background summary

Intravesical instillation of BCG is a widely accepted strategy to prevent recurrence of non muscle invasive bladder cancer. The most accepted treatment schedule is induction of BCG: weeks 1 through 6 plus maintenance (weeks 1,2,3)

at months 3,6 and 12, but it is unknown how many administrations are really necessary. Scientific evidence prones to the hypothesis that after an initial sensitization to BCG antigens has occurred the number of instillations can be reduced for a proper anamnestic immune response resulting in similar clinical efficacy and potentially less side-effects and costs.

Study objective

The primary objective of this study is to identify if reduced number of BCG instillations are not inferior to standard number and dose intravesical BCG treatment in patients with high grade NMIBC. The primary endpoint for inferiority analysis is time to first recurrence.
The secondary objectives are to identify if number and grade of recurrent tumors, rate of progression to a higher stage (T2 or higher) of the disease and safety, specifically the presence of treatment related toxicity > grade 2 differ between the two study arms.

Study design

This is a multicentre prospective, randomized, parallel group, not blinded, trial to compare the efficacy and safety of two different adjuvant treatment schedules:
1) Induction cycle BCG-full dose; weeks 1 through 6 plus maintenance cycles at months 3, 6 and 12 (wks 1,2,3); total 15 full dose BCG instillations
2) Induction cycle BCG-full dose (reduced frequency); weeks 1,2, and 6 plus maintenance cycles at months 3, 6 and 12 (wks 1,3); total 9 full dose BCG instillations.
BCG intravesical instillation therapy is registered as adjuvant treatment for the prevention of recurrence of NMIBC and can be considered as standard treatment for the type of patients requested in this trial. For each individual centre, one of the three locally available BCG strains in Europe will be used: BCG Tice, BCG Medac or BCG Connaught.

• In case of patients having Ta high grade tumor in the initial resection; a) patients can be included in the study provided muscle is present and reported in the specimen and the Ta high grade tumor has been totally removed, or b) patients undergo a re-TUR at the discretion of the investigator.
• Patients having T1 high grade tumor in the initial resection, should undergo a re-TUR. Patients with histological detection of T1 tumor in the re-TUR should undergo a second re-TUR. These patients are eligible for the study provided muscle is present and reported in the specimen and the patients are, macro¬scopically and histologically confirmed, free of T1 tumors in the (re-)re-TUR specimen.

A re-TUR (or re-reTUR) should be performed within 4-8 weeks after initial

resection (or re-TUR).

Treatment with the randomised treatment schedule will start 2 weeks after and no later than 6 weeks after the last resection (re-TUR).
The first maintenance therapy should be given 3 months (12 weeks) after the last instillation of the induction BCG cycle (week 6) and hereafter at months 6 (24 weeks) and 12 (48 weeks) after the last instillation of the induction BCG cycle (Appendix 13: Checklists). Standard Dose Instillations will take place with 1 vial of BCG. The weekly BCG instillations during induction and maintenance cycles have to be conducted within 7 ± 2 days.Follow up cystoscopy and cytology will be done every 3 months the first 2 years and bi-annually until the fifth year.

Intervention

After randomisation, study objects will have one of the two following different adjuvant treatment schedules:
1) Induction cycle BCG-full dose; weeks 1 through 6 plus maintenance cycles at months 3, 6 and 12 (wks 1,2,3); total 15 full dose BCG instillations
2) Induction cycle BCG-full dose (reduced frequency); weeks 1,2, and 6 plus maintenance cycles at months 3, 6 and 12 (wks 1,3); total 9 full dose BCG instillations.

Study burden and risks

The burden and risks associated with participation in the study is considered minimal and acceptable. The number of visits and treatments is equal to or less compared what patients with these criteria is offered when they are treated on a standard way which is BCG intravesical instillation therapy. Extra in this study are the symptoms and quality of life questionnaires that need to be completed. A potential risk for patients in the reduced frequency arm is that the treatment is less effective with respect to the prevention of recurrence compared to the standard frequency arm. A potential benefit is that side effects, both in quantity and quality, are expected to be less in the reduced frequency arm compared to the standard frequency arm. The risks related to the expected treatment outcome, quality and quantity of side effects of the study medication can be considered as acceptable. Surgical procedures, laboratory and radiological evaluations are not considered extra and are performed according to standard practice or at the investigators discretion for monitoring eventual recurrence or progression of disease. Possible benefit for the patient is that the patient is followed according to the latest standards and guidelines of treatment of NMIBC.
For the optional sub-studies, there is slightly more burden (collection of urine and donation of blood). The risk are are neglible. (See also F6)

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-T1) urothelial papillary carcinoma of the bladder with or without CIS
1.1. Tumors can be primary or recurrent
1.2. Tumors can be single or multiple
2a. In case of a Ta high grade tumor in the initial resection, a re-TUR can be performed at the discretion of the investigator. Initial resection or re-TUR must include the deep resection or cold cup biopsy (deep enough to obtain muscle tisssue) of the (initial) tumor site(s)
2b. In case of a T1 high grade in the initial resection a re-TUR should be performed at weeks 4-8 after initial resection, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tisssue) of the (initial) tumor site(s)
3. Re-re-TUR should be performed at weeks 4-8 after re-TUR in case of histological detection of T1 low/high grade in the re-TUR, which must include the deep resection or cold cup biopsy

(deep enough to obtain muscle tisssue) of the initial tumor site(s)
4. Histopathologically confirmed absence of T1 low/high grade tumor in the re-TUR specimen and/or re-re-TUR specimen
5. All visible papillary tumors must be completely resected
6. If the patient is male, he must use a condom during sexual intercourse during the first week after BCG treatment. If the patient is female, and of childbearing potential, she must practice adequate contraception for 30 days prior to administration of study treatment, have a negative pregnancy test and continue such precautions during all study treatment period and for 3 months after of the last BCG treatment.
7. Signed and dated informed consent form.
8. Patient is clinically fit enough to receive BCG bladder instillations.

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 any tumors in upper urinary tract or in the prostatic urethra at any time
5. Presence of any other histological type of resected tumor other than urothelial carcinoma on the first or second resection
6. Presence of another malignancy within 5 years except for basal cell carcinoma of the skin or localised prostate cancer in active surveillance
7. Presence of pregnancy or lactation
8. Presence of active tuberculosis, any form of immunodeficiency (eg HIV + serology, transplant recipients) and/or any other contraindication of BCG therapy
9. Patients who have received any systemic cytostatic agents or multi-installation intravesical chemotherapy in the last 3 months prior to randomisation. Early postoperative (within 6 hours of resection) single dose chemotherapy is allowed after the first resection. However, it should not be given after (re-)re-TUR if the patient is considered eligible for this study
10. Patients with uncontrollable UTI

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Open (masking not used)

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-12-2013
Enrollment:	160
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bacille Calmette Guérin vaccin

Ethics review

Approved WMO Date:	30-09-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-01-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-07-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-06-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-07-2016
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-11-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-09-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-04-2019
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
EudraCT	EUCTR2010-019181-91-NL
CCMO	NL49845.091.14

Study results

Date completed:	26-03-2020
Results posted:	30-06-2021
Actual enrolment:	111

Summary results
Trial ended prematurely

First publication
11-06-2021