The accuracy of detecting residual disease following neo-adjuvant chemotherapy in patients with muscle-invasive bladder cancer

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To assess whether a complete pathological respons (cPR) after neo-adjuvant chemotherapy can be predicted based on clinical, radiological, and histological variables and on a wide set of tissue and blood/urine (liquid biopsy) biomarkers (DNA/RNA)....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bladder and bladder neck disorders (excl calculi)
Study type	Observational invasive

Summary

ID

NL-OMON50035

Source
ToetsingOnline

Brief title
PRE-PREVENCYS

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
Bladder cancer, Muscle invasive urothelial cell carcinoma of the bladder

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: KWF subsidie

Intervention

Keyword: - Muscle-invasive bladder cancer, - Neo-adjuvant chemotherapy, - Prediction, - Residual disease

Outcome measures

Primary outcome

The correlation between the clinical response during and after neo-adjuvant chemotherapy (as assessed by clinical variables, radiological imaging, urine cytology and histological examination on peroperative TUR) and the final pathological response in the radical cystectomy (and lymph-node) resection specimen.

Secondary outcome

1. The number of pathological complete responses (defined as ypT0N0 or ypTaN0 disease) after neo-adjuvant chemotherapy,

2. The number of participants in whom RC could have been withheld if clinical response evaluation (CRE) and histological examination of TUR material after neo-adjuvant chemotherapy correctly predicted a pathological complete response,

3. Predictors of complete pathological response such as age, gender, clinical tumor stage, histological subtype, tumor size, radiological imaging, and a wideset of tissue and liquid biopsy genetic biomarkers.

Study description

Background summary

Muscle-invasive bladder cancer (MIBC) is a highly aggressive disease with a 5-year mortality rate of 40-50%. The gold standard of treatment of MIBC is neo-adjuvant chemotherapy plus radical cystectomy (RC), especially in those with advanced stage disease. Interestingly, it is observed that following neo-adjuvant chemotherapy and after RC, a subset of patients (approximately 20-40%) has no evidence of disease in the resected bladder or in the resected lymphnodes. It might well be that a subset of patients following neo-adjuvant chemotherapy might not benefit from radical surgery. These patients are candidates for bladder preservation and active, close surveillance. For now, it is not yet possible to properly identify patients in whom radical surgery could be withheld.

In recent years, research is done on different predictive and prognostic factors determined in tissue, blood, and urine and that may influence the outcome of neo-adjuvant chemotherapy with respect to pathological complete response. Somatic mutations, mutational burden, and molecular subtypes are associated with a favorable response to neo-adjuvant chemotherapy or otherwise, to chemoresistance.

Study objective

To assess whether a complete pathological respons (cPR) after neo-adjuvant chemotherapy can be predicted based on clinical, radiological, and histological variables and on a wide set of tissue and blood/urine (liquid biopsy) biomarkers (DNA/RNA).

The results of this study will inform us about the number and percentage of patients with a cPR after neo-adjuvant chemotherapy and will help to estimate the number of patients needed for a subsequent randomized controlled trial. The future so-called PREVENCYS trial will randomize patients into 2 strategy groups: (1) neo-adjuvant chemotherapy plus surgery, and (2) neo-adjuvant chemotherapy followed by an active surveillance.

Study design

Prospective multicenter cohort study, 36 months of inclusion

Study burden and risks

1. All participants will be asked to give 2 extra tubes of blood (approximately 30 mL) and urine during regularly foreseen blood collections at clinical and

outpatient visits. Urine is collected at similarly planned visits. These tissue collections are scheduled (1) before start of neo-adjuvant chemotherapy at the time of first diagnosis, (2) after completion of all four neo-adjuvant chemotherapy cycles.

2. There are no additional site visits foreseen.

3. No questionnaires will be delivered.

4. Just prior to RC on the day of surgery with the patient under general anesthesia, participants will undergo per-operative cystoscopy with bimanual examination and TUR/biopsy of all visible lesions and/or scar tissue. This is different than regular care. The risks of complications of this procedure (e.g. marginal bleeding/bladder perforation) are negligibly low as the bladder is also resected (by radical cystectomy) in the same procedure. The total operation time will probably be increased by an estimated 30 minutes with a total regular operating time of RC of 4 to 5 hours.

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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

- 18 year and older,
- Able to understand patient information form (PIF),
- Written informed consent, on study participation and genomic testing,
- Histological diagnosis of MIBC, i.e. cT2-T4a, WHO G1-G3 grade urothelial cell carcinoma of the bladder, locally confined or locally advanced,
- Predominant histology is urothelial cell carcinoma (>50%),
- No evidence of regional or distant metastases, except for a single node in the surgical template of extended pelvic lymph-node dissection (cN1), on staging FDG-PET/CT before initiation of neo-adjuvant chemotherapy,
- Indication for neo-adjuvant chemotherapy and RC, as determined by local multidisciplenary board,
- Cisplatinum-based chemotherapy, i.e. ddMVAC or Gem-Cis per local hospital protocol,
- Clinical response evaluation (CRE) by CT abdomen/thorax with contrast after the second cycle of neo-adjuvant chemotherapy (CRE1), and after completion of neo-adjuvant chemotherapy (CRE2) should show stable disease or a partial local radiological response (subgroup 1),
- CRE1 or CRE2 by CT scanning should show no evidence of residual tumor disease (a complete radiological response), which is defined as pelvic lymph nodes <10 mm in diameter showing no contrast enhancement and a bladder wall of <10 mm showing no contrast enhancement (RECIST criteria)(subgroup 2),
- CRE1 or CRE2 by CT scanning should show no evidence of pulmonary, osseous, he-patic, or non-regional lymph-node metastases.

Exclusion criteria

- Not being able to receive neo-adjuvant chemotherapy as determined by the Galsky criteria,
- Received less than three cycles of cisplatin-based chemotherapy,
- Not being able to undergo RC,
- Concomitant extensive CIS at diagnosis,
- Poor kidney function, under 60 ml/min/kg,
- Concomitant tumors of the upper urinary tract,
- Tumors of the urachus
- A known additional malignancy with the exception of basal cell carcinoma of

the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma), cervical cancer in situ that have undergone potentially curative therapy,

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-11-2020
Enrollment:	180
Type:	Actual

Ethics review

Approved WMO Date:	30-01-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	21-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL70863.029.19