CHemotherapy And Sequential ImmunoTherapy for locally advanced urothelial cancer: the CHASIT study

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This study has been transitioned to CTIS with ID 2024-516940-24-00 check the CTIS register for the current data. To demonstrate the benefit of sequential chemo-immunotherapy in increasing the proportion of patients reaching a pathological complete...

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

Summary

ID

NL-OMON53642

Source
ToetsingOnline

Brief title
CHASIT

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
bladder/upper urinary tract/urethra cancer, Urothelial cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Merck,Merck Healthcare KGaA

Intervention

Keyword: pathological response, radical surgery, sequential chemo-immunotherapy with avelumab, urotheelkanker

Outcome measures

Primary outcome

The pathological complete response rate (pCR), defined as the proportion of

patients without residual urothelial cancer in the surgical resection specimen,

stage ypT0N0/ypTisN0.

Secondary outcome

Progression-free, cancer-specific and overall survival at 24 months.

Study description

Background summary

The global incidence of urothelial cancer (UC) is >=300.000 patients/yr and accounts for 165.000 deaths/yr. Patients with locally advanced irresectable, stage cT4bNxM0 or clinically node-positive, stage cTxN1-N3M0, disease have a very poor outcome. However, in selected cases cure is still possible provided that: i) patients experience an adequate response to induction chemotherapy and ii) thereafter, undergo surgery with radical removal of the primary tumor and all locoregional lymph nodes. Nevertheless, the chances of long-term survival in these patients strongly depends on pathology of the resection specimen; a minority of patients (15%) experience a complete pathological response (pCR), meaning absence of residual cancer. Patients who experience a pCR have a 5-year overall survival of 70-80%. Conversely, patients who have residual invasive disease, stage >=ypT2N0, or nodal metastases, stage >ypN0, after induction chemotherapy have a 5-yr overall survival of only 20%. So, there is a clear unmet need to improve the pCR rate and thereby the survival of patients with locally advanced irresectable, stage cT4bNxM0, or clinically node-positive, stage cTxN1-3M0, UC of the bladder or upper urinary tract. To address this need, we propose to conduct a study with induction chemotherapy, which is, in the absence of disease progression, followed by immunotherapy. Thereafter, patients undergo radical surgery with removal of the affected organ and locoregional lymph nodes.

Study objective

This study has been transitioned to CTIS with ID 2024-516940-24-00 check the CTIS register for the current data.

To demonstrate the benefit of sequential chemo-immunotherapy in increasing the proportion of patients reaching a pathological complete response (pCR) at radical surgery in patients with locally advanced irresectable, stage cT4bNxM0, or clinically node-positive, stage cTxN1-N3M0, UC whose disease did not progress on or following completion of platinum-containing chemotherapy.

Study design

A multicenter prospective phase II non-randomized intervention study.

Intervention

All subjects receive three courses of anti-PD-1 immunotherapy with avelumab at a concentration of 800mg q2w, which is followed by radical surgery with removal of lymph nodes and the primary tumor.

Study burden and risks

Subjects receive three cycles of avelumab 800 mg q2w, which is followed by radical surgery with lymph node dissection within 4 to 8 weeks after day 14 of the last cycle of avelumab. Subjects are asked to provide consent for the collection of additional blood and urine samples; a maximum of 14 in two years* time. Collection of additional blood and urine samples is scheduled during blood draw for routine clinical care. In case of disease progression during the study period, subjects must undergo a biopsy of a suspected metastatic site for confirmatory diagnostic purposes and consent is asked to collect one additional sample for research purposes. It is expected that sequential chemo-immunotherapy is more effective, in terms of pCR rate, than monotherapy with chemotherapy, which is the current standard of care in patients with locally advanced irresectable, stage cT4bNxM0, or clinically node-positive, stage cTxN1-N3M0 UC. The hypothesis is that the immune-priming effects of chemotherapy result in an improved response when sequential immunotherapy is administered. Moreover, the selection of UC patients without progressive disease following induction chemotherapy translates in a higher likelihood of benefit as compared to studies that included all-comers. In addition, the toxicity profile of immunotherapy is different from that of chemotherapy but in general it is less toxic with less grade >3 side-effects. Participating hospitals can offer an additional bladder biopsy after finishing chemotherapy. This will depend on the availability and capacity of the participating hospital. Possibilities will be discussed at study initiation or at request of

the participating hospital.

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. Age >= 18 years.
2. Have histologically confirmed urothelial carcinoma of the bladder, upper urinary tract or urethra; a maximum of 50% of aberrant histology is allowed.
3. Have clinical stage cT4bNxM0 or cTxN1-N3M0 as assessed by bimanual examination under anaesthesia, CT scan, MRI scan or PET-CT scan.
4. Have at least stable disease after a minimum of 3 or a maximum of 4 cycles of induction chemotherapy with Cisplatin / Carboplatin + Gemcitabine according to RECIST v1.1.
5. Are fit and willing to undergo radical surgery with removal of lymph node

template including all affected lymph nodes and the primary tumor.
6. World Health Organisation performance status of 0-2.
7. Provide written informed consent.
8. Negative pregnancy test in women with childbearing potential.
9. Adequate bone marrow function, including:
a. Absolute neutrophil count (ANC) >=1,500/mm3 or 1.5 x 109/L;
b. Platelets >=100 x 109/L;
c. Hemoglobin >=5.6 mmol/L (may have been transfused).
10. Adequate renal function, defined as estimated creatinine clearance >=30 mL/min as calculated by the CKD-EPI eGFR.
11. Adequate liver function, including:
a. Total serum bilirubin <= 1.5 x upper limit of normal (ULN);
b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <= 2.5 x ULN.

Exclusion criteria

1. Predominant (>= 50%) non-urothelial carcinoma histology in the diagnostic endoresection specimen of the bladder, urethra or upper urinary tract. 2. Any test for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating acute or chronic infection. 3. Have an estimated creatinin clearance as assessed by the CKD-EPI eGFR of < 30 ml/min. 4. Prior exposure to immune-mediated therapy with exclusion of Bacillus-Calmette Gue*rin intravesical instillations, including but not limited to other anti-CTLA-4, anti PD-1, anti PD-L1, or anti-PD-L2 antibodies. 5. Persisting toxicity related to prior chemotherapy (Grade >2 NCI CTCAE v5.0). 6. A diagnosis of any other malignancy within 2 years prior to inclusion, except for adequately treated basal cell or squamous cell skin cancer or carcinoma in situ of the breast or of the cervix, low grade prostate cancer on surveillance without any plans for treatment intervention, or prostate cancer that has been adequately treated with prostatectomy or radiotherapy and currently with no evidence of disease. 7. <=2 cycles of induction platinum-based chemotherapy received. 8. Progression of disease during or following induction platinum-based chemotherapy, as assessed by RECIST v1.1. 9. Distant metastatic disease. 10. Previous pelvic radiation therapy. 11. Breastfeeding women. 12. Bilateral upper urinary tract urothelial carcinoma. 13. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible. 14. Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism. 15. Active infection requiring systemic therapy. 16. Known severe hypersensitivity reactions to monoclonal antibodies (Grade 3), any history of anaphylaxis, or uncontrolled asthma (ie, 3 or more features of asthma symptom control per the Global

Initiative for Asthma 2015). 17. Known prior or suspected hypersensitivity to avelumab. 18. Current use of immunosuppressive medication, EXCEPT the following: a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection); b. Systemic corticosteroids at (equivalent) doses of maximum 10 mg prednisone; c. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication). 19. Diagnosis of prior immunodeficiency or organ transplant requiring immunosuppressive therapy, or known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness. 20. Vaccination within 4 weeks of the first dose of study treatment and while on trial is prohibited except for administration of inactivate vaccines (for example, inactivated influenza vaccines) or mRNA vaccines (for example, COVID-19 vaccines). 21. Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, and pneumonitis; psychiatric condition including recent (within the past year) or active suicidal ideation or behaviour; or laboratory abnormality that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-02-2023
Enrollment:	58
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bavencio
Generic name:	Avelumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-04-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-10-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-05-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-09-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	21-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-01-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-03-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-06-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
EU-CTR	CTIS2024-516940-24-00
EudraCT	EUCTR2022-000514-33-NL

Register	ID
CCMO	NL80678.078.22