Randomized multi-centre open-label non-inferiority phase 3 clinical trial for patients with a stage IV childhood renal tumour comparing upfront Vincristine, Actinomycin-D and Doxorubicin (VAD, standard arm) with upfront Vincristine, Carboplatin and Etoposide (VCE, experimental arm)

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This study has been transitioned to CTIS with ID 2023-508926-91-00 check the CTIS register for the current data. To determine non-inferiority of preoperative 6 weeks of VCE to VAD in the overall metastatic rapid response rate (MetRR) in newly…

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

Summary

ID

NL-OMON54046

Source
ToetsingOnline

Brief title
Randomet 2017

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Nefroblastoma, Wilms tumour Stage IV

Research involving
Human

Sponsors and support

Primary sponsor: Gesellschaft für Pädiatrische Onkologie und Hämatologie gGmbH
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Children, Nefroblastoma, Renal tumors, Wilms tumours

Outcome measures

Primary outcome

Primary endpoint: % of patients with radiologic complete response (CR) of any metastasis and/or Very Good Partial Response (VGPR) of lung metastasis of childhood renal tumours after 6 weeks of preoperative chemotherapy

Secondary outcome

Secondary endpoint:

• Radiologic response to preoperative treatment:

* Percentage of patients after 6 weeks of preoperative chemotherapy achieving a CR after surgery of metastasis at time of nephrectomy

* Percentage of patients with remaining metastatic disease after surgery that achieve a CR after 9 weeks of adjuvant chemotherapy

* Percentage of patients with complete response +/- VGPR of (pulmonary) metastasis of nephroblastoma after 6 weeks of preoperative chemotherapy + 9 weeks adjuvant chemotherapy.

* Percentage of patients with complete response +/- VGPR of (pulmonary)

metastasis of nephroblastoma after preoperative chemotherapy + 9 weeks adjuvant chemotherapy + metastasectomy

* Percentage of patients with complete response +/- VGPR of (pulmonary) metastasis of nephroblastoma at the end of adjuvant chemotherapy ± metastasectomy ± RT

* Primary tumour volume shrinkage after 6 weeks of preoperative chemotherapy

* Primary tumour volume after 6 weeks of preoperative chemotherapy

Number of metastases at diagnosis and after preoperative treatment

Maximum size of metastasis at diagnosis and after preoperative treatment

• Histologic & molecular response to preoperative treatment:

* Stage distribution of local tumour

* Histologic subtype distribution of local tumour (LR, IR, HR)

* Histologic subtype distribution of resected nodules/metastasis (LR, IR, HR)

* Percentage of blastema and blastemal residual volume in local tumour

* Percentage of patients with <10 ml of blastemal residual volume in resected nephroblastoma after 6 weeks of preoperative chemotherapy

* Percentage of necrosis in local tumour

* Percentage of patients with complete necrosis in resected nodules/metastasis

* Percentage of patients with 1q gain being in CR/VGPR in both arms.

• Treatment burden, complications, side effects and toxicity:

* Percentage of patients requiring pulmonary radiotherapy in first line

* Percentage of patients suffering Grade 3 or 4 ALAT or bilirubin increase during preoperative treatment

* Percentage of patients suffering from SOS during preoperative treatment

according to EBMT criteria

* Percentage of patients suffering any CTCAE Grade 4 or grade 5 toxicity during preoperative chemotherapy.

* Overall duration of preoperative treatment per arm as determined as interval D1 - date of nephrectomy

* Delay in timing of nephrectomy: Percentage of patients with more than 8 weeks since start of preoperative chemotherapy because of toxicity

* Percentage of (peri-)operative complications (haemorrhage, rupture, thromboembolism)

Outcome:

* Event-free survival at 2 and 5 years for the whole cohort and according to study arm (VAD/VCE) and according 1q gain

* Overall survival at 2 and 5 years for the whole cohort and according to study arm (VAD/VCE) and according 1q gain

Study description

Background summary

Childhood renal tumours are among the most frequent childhood tumours and represent about 6% of all childhood tumours. Nephroblastomas (Wilms tumour, WT) account for >85% of all renal tumours of childhood. Their treatment consists of neoadjuvant chemotherapy, (partial) nephrectomy and risk-based adjuvant chemotherapy ± irradiation[76]. For localized tumours, overall survival is >85% except in case of high risk histology. European patients with nephroblastoma have been treated for > 40 years according to SIOP protocols (International Society of Pediatric Oncology) since 1972 with currently 267 centres collaborating internationally within the SIOP Renal Tumour Study Group [SIOP-RTSG].
Recently SIOP-RTSG has published a standard of care treatment guideline SIOP-RTSG Umbrella.

Childhood renal tumours treated according to SIOP protocols are classified and staged according the SIOP Working classification of childhood renal tumours. Children presenting with metastasis at diagnosis are termed Stage IV. Nephroblastoma metastasize predominantly to the lung (95%) and/or the liver (12%) and only in rare cases to the bones or other extra-abdominal sites (<5%) [Furtwängler R., Oral Presentation, GPOH Scientific Summer Meeting 2008]. Pulmonary metastases are visible on conventional imaging in at least 10-13% of nephroblastoma patients, with an additional 4-13% of patients having suspicious nodules on CT-scan only. The treatment of metastatic nephroblastoma consists of neoadjuvant 3-drug chemotherapy (including Actinomycin D, Vincristine and Doxorubicin), nephrectomy, possibly metastasectomy and risk-based adjuvant chemotherapy ± radiotherapy to the flank and/or metastases. With this multimodality treatment long-term survival reaches more than 80%, and is best in the 48-67% of patients with complete resolution of metastasis after preoperative treatment. However, these promising results are bought at the price of a relevant risk of cardiac and pulmonary sequelae due to the use of doxorubicin ± concomitant RT. Ongoing research shows 4-17% of congestive heart failure rates and a not yet reached plateau of subclinical cardiac changes up to 25% in patients treated with higher doses of anthracyclins. Furthermore, hepatic toxicity due to the use of actinomycin-D can be life threatening in form of a sinusoidal obstruction syndrome (SOS).

Study objective

This study has been transitioned to CTIS with ID 2023-508926-91-00 check the CTIS register for the current data.

To determine non-inferiority of preoperative 6 weeks of VCE to VAD in the overall metastatic rapid response rate (MetRR) in newly diagnosed stage 4 childhood renal tumours. The MetRR will include the pulmonary response rate (PRR) and the response rate on non-pulmonary metastasis (NPRR).

Study design

This is a randomized multi-centre open-label non-inferiority phase 3 clinical trial for patients with a stage IV renal tumor comparing upfront Vincristine, Actinomycin-D and Doxorubicin (VAD, standard arm) with upfront Vincristine, Carboplatin and Etoposide (VCE, experimental arm).

If the study achieves its primary objective, that the VCE arm is non-inferior to the VAD arm in terms of Metastatic Rapid Responders, non-inferiority and superiority tests on secondary endpoints will be used as supportive evidence. Power might be too low to show a beneficial effect for these secondary endpoints convincingly.

If the primary objective is not achieved but a beneficial effect is found for

certain secondary endpoints, further studies might help support this indication of a benefit. The study may be stopped e.g. for safety concerns if the VCE arm has unacceptably unfavourable results for (part of) the study endpoints.

Intervention

Randomization between VAD and VCE treatment

Study burden and risks

Blastemal type nephroblastoma represents a subtype which has already been shown to benefit from intensive treatment in SIOP 2001 [77,82]. This highlights the need to identify *high risk*, chemo resistant blastema in order to avoid unnecessary failure of first line therapy. Hence, one aim of the study is to optimise the definition of high risk, *blastemal type* Wilms tumour, which is currently defined according to the crude proportion of resistant blastemal cells that survived pre-operative chemotherapy.

If the primary objective is not achieved but a beneficial effect is found for certain secondary endpoints, further studies might help support this indication of a benefit.The study may be stopped e.g. for safety concerns if the VCE arm has unacceptably unfavourable results for (part of) the study endpoints.

The sponsor and coordinating Investigators will set up an independent data monitoring committee as part of the trial management to ensure appropriate and safe conduct of the trial. For this purpose, the IDSMC will continuously review the trial data and assess the progress, safety data and critical efficacy endpoints of the trial. It will perform risk-benefit assessments in order to weigh possible safety disadvantages against a possible gain in efficacy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

- Children <18 years at date of diagnosis and >3months
- Patients suffering from metastatic renal tumour at initial diagnosis, having at least one circumscript, non-calcified (pulmonary) nodule (or other lesion highly suspicious of metastasis according to criteria for metastatic disease) >=3 mm as determined by chest CT-scan and abdominal CT-scan/MRI (for radiological details please refer to section 12.8).
- Metastatic childhood renal tumour must be confirmed by central review.
- Signed informed consent form(s) prior to study entry according to national guidelines and GCP guidelines
- Understand and voluntarily provide permission (subjects and when applicable, parental/legal representative(s)) to the ICF prior to conducting any study related assessments/procedures
- Able to adhere to the study visit schedule and other protocol requirements
- No pre-existing and ongoing cardiac malfunction disease (insufficiency, malign arrhythmias)
- No pre-existing and ongoing liver function deficiency that is not controllable by substitution

Exclusion criteria

- inability to be followed until two years after treatment
- other chemotherapy prior to enrolment
- Patient and/or parental/legal representative(s) denied randomization
- primary nephrectomy
- histology other than nephroblastoma if confirmed by upfront tumour

biopsy/cutting needle biopsy
- pregnancy or lactation
- Fertile female with child bearing potential and fertile male subjects who refuse using highly effective contraceptive measures
- Treated by any investigational agent in a clinical study within previous 4 weeks
- hypersensitivity to the active substances or other excipients contained in the investigational medical products listed in the summary of product characteristics (SmPC) or Investigators Brochure (IB).
- unwillingness to follow adequate supportive measures including transfusion of blood products if medically needed
- inability to receive chemotherapy according to the protocol, this is particulary true for:
a. acute kidney failure needing dialysis treatment
b. pre-existing peripheral neuropathy
- Active, uncontrolled life threatening Infection (e.g. Acute Hepatitis, Pneumonia, AIDS, Varizella)
- known chromosomal instability/susceptibility (e.g. Fanconi Anemia, Nejjmegen Breakage Syndrome)
- participation in other interventional trials (registration in observational non-interventional studies is acceptable)
- age at start of treatment <3 months or >18 years
- any other medical condition incompatible with the protocol treatment

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2023

Enrollment:	25
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Dactinomycine
Generic name:	Dactinomycine
Product type:	Medicine
Brand name:	Doxorubicin
Generic name:	Doxorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Etoposide
Generic name:	Etoposide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Vincristin
Generic name:	Vincristin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	26-01-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-03-2023
Application type:	First submission
Review commission:	METC NedMec

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	CTIS2023-508926-91-00
EudraCT	EUCTR2018-000533-13-NL
ClinicalTrials.gov	NCT03669783
CCMO	NL74078.041.22