Paediatric Hepatic International Tumour Trial

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This study has been transitioned to CTIS with ID 2024-516110-38-00 check the CTIS register for the current data. Primary Objectives:-To evaluate if the treatment of Low Risk HB can be reduced (Group B1)-To compare different induction treatment...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON50638

Source
ToetsingOnline

Brief title
PHITT

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
livercancer, Livertumor

Research involving
Human

Sponsors and support

Primary sponsor: University of Birmingham
Source(s) of monetary or material Support: Ministerie van OC&W,Europese Unie (Horizon 2020)

Intervention

Keyword: Children, Hepatoblastoma, Hepatocellular, Livertumour

Outcome measures

Primary outcome

-Group B1: Event free survival

-Group C: Event free survival

-Group D2/D3: Event free survival

-Group F: Respons on chemotherapy

Secondary outcome

-Group A1: Event-free survival, overall survival, adherence to surgical guidelines.

-Group A2: Event-free survival, overall survival, chemotherapy related toxicity, hearing loss, adherence to surgical guidelines.

-Group B1: Event-free survival, overall survival, toxicity, chemotherapy-related toxicity, best respons, hearing loss, adherence to surgical guidelines.

-Group B2: Event-free survival, failure-free survival, overall survival, chemotherapy related toxicity, respons, surgical resectability, hearing loss, adherence to surgical guidelines.

-Group C: Event-free survival, failure-free survival, overall survival, toxicity, chemotherapy related toxicity, respons, hearing loss, adherence to surgical guidelines.

-Group D1: Event-free survival, failure- free survival, overall survival, chemotherapy related toxicity, respons, hearing loss, adherence to surgical

guidelines.

-Group D2/D3: Event-free survival, failure-free survival, overall survival,

toxicity, chemotherapy related toxicity, respons, surgical resectability,

hearing loss, adherence to surgical guideliines.

-Group E1: Event-free survival, overall survival, resectability.

-Group E2: Event-free survival, overall survival, chemotherapy related

toxicity, hearing loss.

-Group F: Respons, failure-free survival, overall survival toxicity,

chemotherapy related toxicity, surgical resectability, hearing loss.

Study description

Background summary

Primary liver tumours (hepatoblastoma (HB) and hepatocellular carcinoma (HCC)) in children account
for 1% of paediatric tumours. The incidence, however, has been increasing with improved neonatal
care for preterm infants, who have an increased risk of developing HB. HB has an annual incidence
of 0.8 per million children. HCC is less common in children.

Currently, the 5 year overall survival (OS) for children with HB is variable and ranges from about 50-
100% depending on the disease characteristics. Among those *cured*, current treatment regimens
have a risk of significant toxicities including cisplatin-induced oto-toxicity and nephrotoxicity,
doxorubicin-induced cardiomyopathy and secondary leukaemia. In patients treated for HB with 600
mg/m2 of cumulative cisplatin, hearing loss to the point of requiring augmentation devices occurs in
half of all patients, severely impacting childhood development and quality of life. The lethal impact
of anthracycline-induced cardiomyopathy and secondary leukaemia is self-evident.

The Paediatric Hepatic International Tumour Trial (PHITT) trial will investigate whether reductions in therapy reduce the risk of both short- and long-term side effects for patients with good prognosis without compromising their good outcomes and whether intensifying treatments with the introduction of new agents improves outcomes for those with a poor prognosis.

Study objective

This study has been transitioned to CTIS with ID 2024-516110-38-00 check the CTIS register for the current data.

Primary Objectives:
-To evaluate if the treatment of Low Risk HB can be reduced (Group B1)
-To compare different induction treatment regimens for Intermediate risk HB (Group C)
-To compare different post induction treatment regimens for High Risk HB (Group D2)
-To determine if the outcome is improved when GEMOX is added to PLADO in the treatment of
unresected hepatocellular carcinoma HCC (Group F)
-To collect samples for biological and toxicity studies. (All groups)

Secondary Objectives:
-To report outcome (including event-free survival (EFS), failure-free survival (FFS), overall
survival (OS), toxicity and surgical outcome) in all patient groups.
-To validate a new global risk stratification, defined by Children*s Hepatic Tumours
International Collaboration (CHIC)
-To evaluate clinically relevant factors, including the following:
> Provide a comprehensive and highly-validated panel of diagnostic and prognostic
biomarkers
> Determine if paediatric HCC is a biologically different entity to adult HCC
> Develop genomic and/or biomarker analysis to predict children who may have an increased risk of developing toxicity with chemotherapy.
-To establish a collection of clinically and pathologically-annotated biological samples.
-Evaluate a surgical planning tool for an impact on decision making processes in POST-TEXT
III and IV HB

Study design

The PHITT trial is a collaborative trial involving three major clinical groups running paediatric liver

tumour trials the International Society of Paediatric Oncology Epithelial Liver Tumour Group (SIOPEL),
the Liver Tumour Committee of the Children*s Oncology Group, USA (COG), the Japanese Children*s
Cancer Group (JCCG). The European arm of the study is led by the SIOPEL group and is sponsored by the University of Birmingham, UK and detailed in this protocol. It is anticipated that the other trial groups will use a similar protocol, with an overall analysis of all patients taking place. PHITT is the clinical trial within the Children*s Liver Tumour European Research Network (ChiLTERN) Programme. Biology and pathology research will be done in collaboration with the ChilTERN Programma.

The PHITT is an international, over-arching phase III trial, with four randomised comparisons, for paediatric, adolescent and young adult patients with newly diagnosed HB and HCC.

This trial includes a registration phase (trial entry) where patients will give consent for the analysis of their biological samples, tumour pathology and imaging reports to determine the grading and status of the disease, before being allocated in a Treatment Group.

Patients with HB are classed into four risk-stratified groups and treated using different regimens.
-Group A, very low risk.
Group A1 (WDF-histology); no further treatment.
Group A2 (non-WDF); 2 cycles cisplatin

-Group B, low risk
Group B1 (resected after 2 course cisplatin). Randomisation 2 cycles cisplatin vs. 4 cycles cisplatin
Group B2 (not resectable after 2 course cisplatin). Patients have further standard treatment and surgery.

-Group C, intermediate risk
Group C; Randomisation induction chemo therapy: SIOPEL-3HR vs. 5CVD vs. CDDP-M

-Group D, high risk
Group D1 (good respons or non-metastatic); Further standard treatment Carbo-Doxo
Group D2/D3 (poor respons); Carbo-Doxo alternating with randomised carbo-etop vs. vincr-irinotecan

HCC patients are treated in two risk-stratified groups.
-Group E, completely resected HCC
Group E1 (secondary to underlying liver disease); No further treatment.
Group E2 (de novo HCC); Standard treatment PLADO chemotherapy

-Group F, not resectable HCC

Group F; Randomisation PLADO+S vs. PLADO+S alternating GEMOX+S.

Intervention

Group A: No intervention.
Group B1: Randomisation between 4 additional cycles versus 2 additional cycles cisplatin.
Group B2: No intervention.
Group C: Randomisation between SIOPEL-3HR versus C5VD versus CDDP-M.
Group D1: No intervention.
Group D2: Randomisation between carbo-doxo/carbo-etop versus carbo-doxo/vinc-irinotecan
Group E1: No intervention.
Group E2: No intervention.
Group F: Randomisation between PLADO+S versus PLADO+S alternating with GEMOX+S.

All groups:
In addition to the standard care blood and (tumor)tissue will be collected for biology and pathology research at diagnosis, end of treatment and relapse. This will be done in combination with standard care blood sampling and biopsies. Extra blood and urine will be collected in patients receiving cisplatin, carboplatin or doxorubicin. These samples will be collected for toxicity biomarker research. This will be combined with standard sampling as much as possible.

Study burden and risks

Patients with a liver tumor should be treated to cure. Also in the current standard treatment, patients would be hospitalized for several days. The toxicity and safety will be closely monitored during this study. The treatment is therefore justified.

In groups A and B, we try to reduce the number of courses and reduce the burden in this protocol. The advantage may be that patients have fewer side effects due to this reduction. A disadvantage may be that patients receive not enough treatment. This is still unknown and subject of this study.
Patients will visit the hospital as many days or less.

Three world-wide commonly used standard treatments are compared in group C. It is still unknown which one is the best and this is the subject of this study.
The participant has no direct benefit or disadvantage here.

Two new regimes are added to standard therapy in group D. It may be that this improves the outcome, but that is not proven and subject of this study. The additional medication can cause other or new toxicity. It is possible that the additional medication does not give any improvement.

In group E, patients receive the current standard treatment.

In group F, patients receive additional medication. The advantage may be that this results in a better result in this group with a bad prognosis. However, this is not proven and subject of this study. The disadvantage may be that the additional agents do not give a better result and the medication causes other toxicity. This is justified in patients with this poor prognosis

In addition to the treatment, blood, tissue and urine will be collected for different studies. In the future this can provide valuable information, the participant has no benefit here now. The disadvantage may be that the patient suffers from pain or stress. The decreases are combined as much as possible with regular decreases, interventions and hospitalization. Patients have an access device, that is used for standard care, which keeps the number of injections limited. This part of the study will be terminated if patient oppose or withdraw consent.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

For Trial Entry:
• Clinical diagnosis of HB or histologically defined diagnosis of HB or HCC.
• Age <=30 years
• Written informed consent for trial entryFor Allocation/Randomisation to Treatment Group:
All Groups
• Written Informed Consent for trial treatment participation
• Patient assessed as fit to receive group specific treatment
• For females of child-bearing potential, a negative pregnancy test prior to trial entry is required. Any patient who is of reproductive age must agree to use adequate contraception for the duration of the trial.Group A (no treatment arm)
At diagnosis:
• Resected Tumour.
• Patient meets Very Low Risk definition according to CHIC guidelines.
Group A1 - No treatment arm
• Central pathology review confirming WDF histology.
Group A2 - Treatment arm
• Central pathology review confirming non-WDF histology.
• Adequate renal function
• Adequate hematology / biochemistryGroup B
• Patient meets Low Risk definition according to CHIC Guidelines
• Adequate renal function
• Adequate hematology / biochemistryGroup C
• Patient meets Intermediate Risk definition according to CHIC Guidelines
• Adequate renal function
• Adequate cardiac function
• Adequate hematology / biochemistry

Group D
• Patient meets High Risk definition according to CHIC Guidelines
• Adequate renal function
• Adequate cardiac function
• Adequate hematology / biochemistry

Group E
• Patient has been diagnosed with HCC

• Tumour has been locally assessed as resectable
• Adequate renal function
• Adequate cardiac function
• Adequate hematology / biochemistryGroup F
• Patient diagnosed with HCC
• Tumour locally assessed as un-resectable, or metastatic HCC disease
• Adequate renal function
• Adequate cardiac function
• Adequate hematology / biochemistrySee protocol paragraph 4 for the definitions of adequate organ function

Exclusion criteria

• Any previous chemotherapy or currently receiving anti-cancer agents
• Recurrent disease
• Previously received a solid organ transplant
• Uncontrolled infection
• Unable to follow the protocol for any reason
• Second malignancy
• Pregnant or breastfeeding womenGroup specific exclusion criteria
All Groups:
-Hypersensitivity to any medicines used in allocated group. Group C:
-Patients who have known deficiency of dihydropyrimidine dehydrogenase (DPD)
Group D:
-Chronic inflammatory bowel disease and/or bowel obstruction
-Concomitant use with St John*s Wort which cannot be stopped prior to start of trial treatment Group F:
-Low K, Mg or Ca which remains uncorrected by electrolyte supplementation
-Peripheral Sensory Neuropathy with functional impairment
-Personal or family history of congenital long QT syndrome
-QT/QTc interval >450msec for males and >470msec for females
-Patients who are unable to swallow tablets where an oral suspension is not available or not approved
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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:	Recruiting
Start date (anticipated):	30-07-2019
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	5-Fluorouracil
Generic name:	5-Fluorouracil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Cispatin
Generic name:	Cisplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Doxorubicin
Generic name:	Doxorubicin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Vincristin
Generic name:	Vincristin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	09-01-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-03-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-11-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	08-01-2021
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

ID: 25549
Source: NTR
Title:

In other registers

Register	ID
Other	17869351
EU-CTR	CTIS2024-516110-38-00
EudraCT	EUCTR2016-002828-85-NL
CCMO	NL62546.078.18