European Paediatric Soft Tissue Sarcoma Study Group RMS 2005 - a protocol for non metastatic rhabdomyosarcoma

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Soft tissue neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON29994

Source
ToetsingOnline

Brief title
EpSSG-RMS-2005

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
Rhabdomyosarcoma, tumor of striated muscle

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: non metastatic rhabdomyosarcoma

Outcome measures

Primary outcome

The primary endpoint of both randomizations is EFS.

Secondary outcome

Secondary endpoints are Overall Survival, Progression Free Survival, Respons

Rate (RR), and Toxicity.

Study description

Background summary

In The Netherlands yearly 20 children are diagnosed with a rhabdomyosarcoma (RMS). RMS is the commonest form of soft tissue sarcoma in children and accounts for approximately 6% of all childhood malignancy. The prognosis of children with localized rhabdomyosarcoma has improved dramatically since the introduction of co-ordinated multimodality treatment. Cure rates have improved from 25% in the early seventies, when combination chemotherapy was first implemented, to approximately 70% in more recent years.
Approximately 50% of children with RMS have unfavorable prognostic characteristics. These patients are stratified in the High Risk Group (HRG). Prognosis of patients in the HRG with current therapy is only 50%. Therefore new treatment strategies have to be developed to improve the prognosis for this large subgroup
Standard chemotherapy for the HRG consists of 9 courses of multidrug chemotherapy, a combination of Iphosfamide, Vincristin and Actinomycin-D (IVA). High risk patients are eligible for two sequential randomizations:

The first randomisation concerns the addition of Doxorubicin to the first 4 standard IVA chemotherapy courses. This allows intensification of induction chemotherapy with Doxorubicin, an agent that has shown to be very effective as single agent in RMS patients (respons rate [RR] of 65% in an up-front window setting).

The second randomization concerns the addition of maintenance treatment for HRG patients who are in complete remission after standard treatment (estimated to

be about 80% of patients in the HRG). The concept of maintenance treatment is based on a German trial for children with metastatic RMS, that showed (in a center based randomization) that adding maintenance therapy to standard therapy was more effective than adding high dose chemotherapy with stem cell rescue (event free survival [EFS] 50% and 20% respectively). The total duration of maintenance therapy is 6 months. Maintenance therapy encompasses a daily oral dose of cyclophosphamide (an agent that has proven to be effective in RMS). Furthermore patients will get weekly gifts of intravenous vinorelbine on a day care basis. After every third weekly gift of vinorelbine there will be a week rest, resulting in a total number of 18 doses of vinorelbine. Vinorelbine is a promissing agent in RMS treatment as it has been shown to have a RR of 30-50% in heavily pretreated patients.

Both randomizations are part of a Pan-European trial, also encompassing several non-European countries. The Dutch Childhood Oncology Centers have decided to include their patients in this European trial (Decision Dutch Childhood Oncology Group d.d. september 9, 2005).

Study objective

During the course of the study 2 randomisation questions will be adressed. Both questions concern patients in the high risk group.

Randomisation question 1: Will the addition of Doxorubicin to the first 4 standard IVA chemotherapy courses lead to a better survival for patients in the high risk group? (Intensification question).

Randomisation question 2: Will the addition of maintenance treatment for HRG patients who are in complete remission after standard treatment lead to a better survival for patients in this group?

Study design

Observational study with double randomisation

Intervention

Randomisation 1: in the intervention group Doxorubicin will be added to the first 4 standard IVA chemotherapy courses. Per IVA-chemotherapy course a patient will get 2 gifts of Doxorubicine of 30 mg/m2 each on day 1 and day 2. Patients in the control group will get standard IVA-chemotherapy courses.

Randomisation 2: The total duration of maintenance therapy is 6 months. Patients in the intervention group will get maintenance therapy, encompassing a daily oral dose of cyclophosphamide 25 mg/m2 for a total duration of 24 weeks. Furthermore patients in the intervention group will get weekly gifts of

intravenous vinorelbine 25 mg/m2. After every third weekly gift of vinorelbine there will be a week rest, resulting in a total number of 18 doses of vinorelbine. Patients in the control group will not get maintenance therapy after standard IVA-chemotherapy.

Study burden and risks

The IVA-Doxorubicin regimen was piloted and showed a RR of 84% with acceptable toxicity. Intensifying induction therapy might lead to a higher incidence of infections or an increase of the need for blood transfusions. Because of this patients might spend more days in hospital.
The chances for cardiotoxicity adding Doxorubicin in a cumulative dose of 240 mg/m2 are low. Furthermore cardiac function will be monitored according to the protocol.
Given the relatively poor prognosis of RMS patients in the HRG, the possible chances for a better prognosis outweigh the low risk for possible negative side effects.

The combination of Vinorelbine and Cyclophosphamide was piloted in a phase 2 study, was well tolerated, and appeared to have a RR of 38% in heavily pretreated patients. Maintenance treatment is given on an outpatient basis, and does not add any important risks for a patient group that might benefit from an improvement of survival.

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)

Inclusion criteria

Patients with pathologically confirmed rhabdomyosarcoma
No evidence of metastatic disease
Age 6 months - < 21 years
Included in the High Risk Group

Exclusion criteria

Previously treated except initial surgery
Pre-existing illness preventing treatment
Previous malignant tumor

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:	Recruitment stopped
Start date (anticipated):	10-08-2006
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Doxorubicin
Generic name:	Adriamycin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Endoxan
Generic name:	Cyclophosfamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Navelbin
Generic name:	Vinorelbin
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Application type:	First submission
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
EudraCT	EUCTR2005-000217-35-NL
CCMO	NL11925.018.06

Study results

Date completed: 31-12-2017

Actual enrolment: 98

Summary results
Trial is onging in other countries