

EWING 2008

Published: 12-09-2011

Last updated: 27-04-2024

Primary objectives: Standard Risk R1: in a randomised trial, to examine whether add-on treatment with fenretinide or zoledronic acid, or zoledronic acid plus fenretinide in addition to induction and maintenance chemotherapy improves event-free...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skeletal neoplasms malignant and unspecified
Study type	Observational non invasive

Summary

ID

NL-OMON46854

Source

ToetsingOnline

Brief title

EWING 2008

Condition

- Skeletal neoplasms malignant and unspecified

Synonym

bone tumour, Ewing sarcoma

Research involving

Human

Sponsors and support

Primary sponsor: Stichting Kinderoncologie Nederland

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: bone tumour, chemotherapy, Ewing sarcoma, malignancy

Outcome measures

Primary outcome

Outcome:

To analyse outcome (EFS, OS) of the entire group of patients.

Quality of life: To describe the quality of life (QOL) longitudinally (i.e. during the course of treatment and thereafter) in patients and to determine the impact on QOL of the additional treatment (R1 and R3) after randomisation for consolidation treatment. Also when R2 patients have to remain consistent with EURO-E.W.I.N.G. 99, the assessment of QOL within the current trial does not violate any of the basic codes of practice defined within this treatment protocol.

Value of Positron Emission Tomography: To examine the value of positron emission tomography in the diagnosis and treatment response of Ewing sarcomas.

Time to Diagnosis: To investigate the impact of the time to diagnosis on the presentation and outcome of the patients.

Add-on studies:

Pharmacogenetic study:

SNP-analysis data correlated with response and outcome data

Secondary outcome

-

Study description

Background summary

EWING 2008 is a joint protocol of European and North American Ewing sarcoma study groups. The protocol is aimed at optimising treatment and treatment results of patients with Ewing sarcomas. The EWING 2008 protocol is open to all patients diagnosed with Ewing sarcomas, localised or metastatic, who are considered eligible for neoadjuvant chemotherapy. All patients registered will receive induction chemotherapy consisting of six cycles of vincristine, ifosfamide, doxorubicin and etoposide (VIDE). The decision regarding local therapy must be made following the fifth cycle of induction treatment, with a preference for surgical intervention with or without additional radiotherapy. Preoperative radiotherapy may be considered to improve the operability of otherwise inoperable lesions. In patients with localised disease or with pulmonary metastases, local treatment should be performed following the 6th cycle of VIDE chemotherapy, and should be a complete tumour resection, whenever feasible. Post-operative radiotherapy is determined by the completeness of surgery and the histological response to chemotherapy.

Standard Risk R1

Good responders (R1) (< 10% viable tumour cells) with localised disease are allocated to the standard risk arm and will receive a further eight cycles of chemotherapy composed of vincristine, actinomycin D, and cyclophosphamide (VAC) (females) or ifosfamide instead of cyclophosphamide (VAI) (males). They will be randomised to receive add-on treatment with either fenretinide, zoledronic acid, fenretinide plus zoledronic acid, or no add-on treatment. The fenretinide arm is still closed since the drug is not available and the formulation is still unknown. Therefore an amendment for this part of the study will be handed in later.

High Risk R2 (closed per december 2015)

Poor responders (R2) with localised disease will continue to be randomised as in EURO-E.W.I.N.G. 99 to receive either eight cycles of VAI chemotherapy or high dose treatment with busulfanmelphalan (R2loc). Patients with primary pulmonary metastases are also allocated to continue to be randomised as in EURO-E.W.I.N.G. 99 to receive either eight cycles of VAI chemotherapy or high dose treatment with busulfan-melphalan (R2pulm).

Very High Risk R3

Patients with disseminated disease, i.e. dissemination to bone and/or other sites and possibly additional pulmonary dissemination (R3), receive six cycles of VIDE induction chemotherapy. Patients are then randomised to either continue with eight cycles of vincristine, actinomycin D and cyclophosphamide (VAC) chemotherapy or high dose treosulfan-melphalan (TreoMel) chemotherapy followed by autologous stem cell reinfusion followed thereafter by eight cycles of VAC chemotherapy. Local therapy in R3 patients is following VIDE induction, whenever feasible prior to high dose therapy (HDT). When long periods of immobilisation following surgery are anticipated, e.g. pelvic reconstruction, surgery following HDT may be advisable. Depending on clinical response to induction chemotherapy radiotherapy prior to HDT and surgery may be an option to be considered in such patients. Any delay between VIDE and HDT for reasons of e.g. local treatment must be bridged with VAC cycles. The total number of VAC cycles is not to exceed eight cycles.

Add-on study:

Pharmacogenetics

Genetic polymorphisms of metabolic enzymes active in cytostatic drugs are related in part with outcome of anti-tumour treatment. This study aims to correlate such data for Ewing tumours. On the long run this study might enable tailored therapy for Ewing tumour patient increasing efficacy and reducing toxicity.

Amendment:

Randomisations are halted.. Studie is only a registry of patients receiving conventional therapy

Study objective

Primary objectives:

Standard Risk R1: in a randomised trial, to examine whether add-on treatment with fenretinide or zoledronic acid, or zoledronic acid plus fenretinide in addition to induction and maintenance chemotherapy improves event-free survival in patients with localised Ewing sarcoma and good histological response or with initial tumour volume <200ml compared to no add on treatment. The fenretinide part of this study will be submitted for assessment at a later stage.

High Risk R2: in a randomised trial, to examine whether high dose chemotherapy using busulfan-melphalan with autologous stem cell reinfusion, compared with standard chemotherapy, improves event-free survival in patients with localised Ewing sarcoma and unfavourable histological response or tumour volume >200ml (R2loc). In patients with pulmonary metastases high dose busulfan-melphalan chemotherapy with autologous stem cell reinfusion is randomised versus standard chemotherapy plus whole lung irradiation (R2pulm).

Very High Risk R3: in a randomised trial, to examine whether the addition of high dose chemotherapy using treosulfanmelphalan followed by autologous stem

cell reinfusion to eight cycles of standard adjuvant chemotherapy, compared to eight cycles of standard adjuvant chemotherapy alone, improves event-free survival in patients with primary disseminated disease.

Secondary objectives:

Overall survival

R1: To investigate whether add-on fenretinide, zoledronic acid or zoledronic acid plus fenretinide improves overall survival compared to no add-on treatment.

R2: To investigate whether high-dose chemotherapy with busulfan-melphalan improves overall survival.

Toxicity /Safety: To evaluate short-term toxicity and long-term toxicity in all risk groups.

Add-on study:

Pharmacogenetics

This study aims to correlate pharmacogenetic data for Ewing tumours. On the long run, this study might enable tailored therapy for Ewing tumour patients, increasing efficacy and reducing toxicity.

Amendment:

Randomisations are halted.. Study is only a registry of patients receiving conventional therapy

Study design

Registration: * 45 days after diagnostic biopsy.

Reference pathology: * 60 days after diagnostic biopsy.

Radiol. response evaluation: After VIDE 2 (earliest) or 3 (latest), After VIDE 5 (earliest) or 6 (latest), Prior to high-dose chemotherapy, Prior to add-on in R1, i.e. after cycle 11 of chemotherapy, e.g. 6 VIDE + 5 VAI/VAC.

Stem cell harvest: After 3-4 cycles of VIDE.

Surgery for primary tumour: After 6 cycles of VIDE, In R3 patients prior to or after HDT.

Randomisation:

R1 and R2: After 6 cycles of VIDE when histology is available.

R1 and R2: Latest after 6 cycles of VIDE when surgery is not indicated.

R3: Latest after 6 cycles of VIDE.

Surgery for metastases: After 2 cycles of consolidation treatment or after high-dose treatment.

Definitive radiotherapy: After 6 cycles of VIDE parallel to consolidation

chemotherapy, In R3 patients prior to or after HDT.

Pre-operative radiotherapy:

Prior to surgery. Post-operative radiotherapy: Concurrently with consolidation chemotherapy. In patients receiving HDT, 8-10 weeks after HDT.

Quality of Life assessment: After VIDE 1 (earliest) or 2 (latest), After VIDE 6 (prior to local treatment), After completion of protocol treatment, After 2 years follow-up.

Add on study:

Pharmacogenetic study;

On 10 ml peripheral blood SNP analysis will be done and will be correlated with response and outcome data.

Immunological study:

NK- and T-cells will be generated on 2 occasions (prior to start of chemotherapy and after finishing treatment). Activity against Ewing cells, will be studied using Ewing cells obtained at the diagnostic biopsy done to confirm the diagnosis of Ewing tumors.

Amendment:

Randomisations are halted.. Studie is only a registry of patients receiving conventional therapy

Intervention

R1 patients.

Standard chemotherapy will be given. After local therapy 10 infusion with zoledronic acid will be given.

R2 patients:

The standard seven courses of consolidation therapy are exchanged with high dose chemotherapy and autologous stemcell rescue.

R3 patients

Additional high dose chemotherapy with autologous stem cell rescue.

Add-on study:

no interventions

Study burden and risks

Patients will be treated according to normal standard currently used in Ewing sarcoma. In respect to this study the following changes should be mentioned

R1 patients.

Standard chemotherapy will be given. After local therapy 10 infusion with zoledronic acid will be given at standard moments of check-up at the physicians office / hospital. In total this will be add a 5 to 10 hours to the total standard treatment. The medication will be given over an already existing permanent intravenous device, so pain and discomfort will be minimal. Side effects will be low frequent and will be monitored. Benefit can be improvement of survival.

R2 patients: (closed per December 2015)

The standard seven courses of consolidation therapy are exchanged with high dose chemotherapy and autologous stemcell rescue. Total hospitalization in respect to numbers of days of admission will be equal. The side effects of the high dose therapy can be more pronounced, however, this can outweigh the side effects during the prolonged period of the seven intensive chemotherapy courses that would have been administered. Benefit can be an improved survival.

R3 patients

Additional high dose chemotherapy with autologous stem cell rescue. Risks are related to the well known side effects of intensive chemotherapy. Benefit can be an improved survival in these patients with otherwise a very poor outcome.

Add-on

Pharmacogenetic study:

10 ml blood sampling at the moment of regular blood sampling

Amendment:

Randomisations are halted.. Studie is only a registry of patients receiving conventional therapy

Contacts

Public

Stichting Kinderoncologie Nederland

Postbus 43512

Den Haag 2504AM

NL

Scientific

Stichting Kinderoncologie Nederland

Postbus 43512

Den Haag 2504AM

NL

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

- Histologically confirmed Ewing tumour of bone or soft tissue. ; - Either sex, age >48 months (for GPOH patients) and <50 years at the date of diagnostic biopsy.;- Registration within 45 days after diagnostic biopsy/surgery.;- Start of chemotherapy within 45 days after diagnostic biopsy/surgery.;- Informed consent signed prior to study entry. ; - Lansky or Karnofsky score > 50%, may be modified for handicapped patients.;- Haemoglobin > 8 g/dl, Platelets > 80.000/ μ l, WBC > 2000/ μ l.;- LVSF > 40%, FS >28%.

Exclusion criteria

- More than one cycle of chemotherapy prior to registration;- Second malignancy;- Pregnancy and lactation;- Any other medical, psychiatric, or social condition incompatible with the protocol treatment

Study design

Design

Study type: Observational non invasive

Masking: Open (masking not used)

Control: Uncontrolled

Primary purpose: Other

Recruitment

NL

Recruitment status: Recruitment stopped

Start date (anticipated): 18-10-2011

Enrollment: 87

Type: Actual

Ethics review

Approved WMO

Date: 12-09-2011

Application type: First submission

Review commission: METC Amsterdam UMC

Approved WMO

Date: 04-09-2012

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO

Date: 09-04-2013

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO

Date: 14-11-2013

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO

Date: 17-06-2015

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO

Date: 05-08-2015

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO

Date:	10-06-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	
Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	
Date:	04-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	
Date:	25-09-2018
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
EudraCT	EUCTR2008-003658-13-NL
CCMO	NL31313.018.11