INTERNATIONAL RANDOMIZED PHASE II TRIAL OF THE COMBINATION OF VINCRISTINE AND IRINOTECAN WITH OR WITHOUT TEMOZOLOMIDE (VI OR VIT) IN CHILDREN AND ADULTS WITH REFRACTORY OR RELAPSED RHABDOMYOSARCOMA

Published: 10-06-2011
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Primary:- To evaluate the efficacy of the combination of temozolomide with vincristine and irinotecan in children and adult patients with relapsed rhabdomyosarcoma as assessed by confirmed objective tumor response.Secondary:- To evaluate the safety...

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

Summary

ID

NL-OMON47843

Source
ToetsingOnline

Brief title
VIT-0910

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
Rhabdomyosarcoma

Research involving
Human

Sponsors and support

Primary sponsor: Centre Oscar Lambret
Source(s) of monetary or material Support: Stichting 'GO4Children'

Intervention

Keyword: Irinotecan, Randomized phase II trial, Rhabdomyosarcoma, Temozolomide

Outcome measures

Primary outcome

The primary efficacy endpoint is defined as the proportion of patients who had a documented complete or partial tumour response occurring after the first 2 cycles of treatment which must be confirmed by a follow-up objective tumour assessment obtained within 4-5 weeks after the initial documentation.

Secondary outcome

Secondary efficacy endpoints are defined as follows:

- Duration of tumour response: the time from first documentation of objective tumour response to the first objective or clinical documentation of progression

- Time to treatment failure: the time from the date of first treatment administration to the first documentation of tumour progression, discontinuation of study treatment before one year, or death, whichever occurs first

- Time to tumor progression: the time from the date of first treatment administration to the date of first objective or clinical documentation of tumour progression or death due to any cause

- Overall survival: the time from the date of first treatment administration to

date of death

Study description

Background summary

Rhabdomyosarcoma is a soft tissue sarcoma derived from muscle precursor cells. It is the commonest form of soft tissue sarcoma in children < 15yrs, accounting for around 4% of paediatric malignancies and with a peak incidence in young children < 5yrs.
Around 85% of children with rhabdomyosarcoma have localised disease at presentation. The 3 yr event free survival of patients achieving complete local control is 64% and 36% of patients who relapse can be salvaged. Among patients experiencing relapse, the most frequent site of relapse is locoregional (76%) with only 15% of patients having an isolated metastatic recurrence. Survival after relapse is affected by several factors, the most important being the type of recurrence, previous radiotherapy, time of relapse and the initial tumour size. Survival after an isolated local relapse is around 50% at 3 years whereas it is only 13-14% at 3 years after a metastatic relapse. This finding means that we urgently need new chemotherapy agents and/or targeted agents for systemic treatment of rhabdomyosarcoma. Another key factor is the ability to deliver good local therapy to locally relapsing tumours; where patients have previously received radiotherapy, local therapy may be limited to aggressive surgery. Surgical clearance may be aided by effective new systemic therapies justifying the use of volumetric response of the target lesions to the chemotherapy as the main evaluation criteria in the current study.
The combination of Vincristin and Irinotecan is attractive as it has proven it's activity in naive metastatic patients (window response rate 70%). In a relapse setting response rate was 25-37%. Cytotoxicity of Irinotecan is potentiated by Temozolomide and the toxicity profile of Temozolomide does not show important overlap with the toxicity profiles of Irinotecan or Vincristine.
In preclinical studies (xenograft models of among others rhabdomyosarcoma) complete responses were shown after combinations of non curative doses of each drug suggesting therapeutic synergy. In successive pediatric phase I trials dose limiting toxicities and maximum tolerated dose of Temozolomide and the combination of Irinotecan, Temozolomide and Vincristine were determined. The proposed trial will investigate the efficacy and tolerability of the addition of Temozolomide (VIT) to the combination of Vincristine-Irinotecan (VI) in refractory or recurrent rhabdomyosarcoma.

Study objective

Primary:

- To evaluate the efficacy of the combination of temozolomide with vincristine and irinotecan in children and adult patients with relapsed rhabdomyosarcoma as assessed by confirmed objective tumor response.

Secondary:
- To evaluate the safety, tolerability and efficacy of VIT and VI alone as assessed by: duration of response, time to tumor progression, time to treatment failure, overall survival and adverse event profile.

Study design

This is an international open-label, randomized, multicenter phase II study of VIT and VI for the treatment of patients with recurrent rhabdomyosarcoma.

Intervention

Patients will be randomized 1:1 between treatments. Standard arm will be VI: combination of Vincristin (intravenous day 1 and 8) and Irinotecan (intravenous day 1 - 5). Intervention arm will be the standard arm (VI) with the addition of oral Temozolomide (day 1 - 5) (VIT). Both the standard and intervention treatment arm will be given in a daycare setting. Patients will be treated with cefixim day -2 till day 7 according to international guidelines.

Study burden and risks

The combination of Vincristin-Irinotecan is currently regularly applied in patients with a relapsed rhabdomyosarcoma outside the setting of a prospective therapeutic trial. This combination is chosen based on expected effectivity and toxicity profile, where bone marrow suppression is not frequently found. Important toxicity of Irinotecan is diarrhea, where chances for diarrhea are reduced by the profylactic administration of ceftibuten. In case of diarrhea this can usually be adequately treated with loperamide.
The addition of Temozolomide to Vincristin and Irinotecan was well tolerated in earlier trials. Most important expected toxicity of Temozolomide is bone marrow suppression, possibly causing the need for blood transfusions and risk for infections.
All 3 drugs (Vincristin, Irinotecan and Temozolomide) can cause nausea; with the profylactic use of antiemetics, nausea is generally well controlled.

Contacts

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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

• Histologically or cytologically confirmed diagnosis of rhabdomyosarcoma
• Relapsed / progressive disease (previously shown respons to chemo-therapy)
• Measurable disease (defined as lesions that can be measured in 3 dimensions by medical imaging techniques such as CT or MRI).
• Age > 6 months and <=50 years
• Karnofsky performance status (PS) 70-100% (for patients > 12 years of age)
OR Lansky Play Score 70-100 % (for patients <= 12 years of age)
• Life expectancy >= 12 weeks
• Adequate bone marrow-, renal- and hepatic function (as defined in protocol)
• Fertile patients must use effective contraception
• Written informed consent of patient and/or parents/ guardians

Exclusion criteria

• Other malignancy, including secondary malignancy
• Concomitant anti-cancer treatment
• Pregnancy or breast feeding
• Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
• Neuromuscular disorders (e.g. Charcot-Marie Tooth disease)
• Uncontrolled intercurrent illness or active infection
• Unavailable for medical follow-up (geographic, social or psychological reasons)
• Concurrent enzyme-inducing anticonvulsants (EIAC), including phenytoin, phenobarbital, or carbamazepine
• Concurrent administration of any of the following: rifampicin, voriconazole, itraco-nazole, ketoconazole, aprepitant
• Prior irinotecan or temozolomide administration
• Less then 3 weeks since prior myelosuppressive therapy (6 weeks for nitrosourea, 2 weeks for vincristine, vinorelbine, vinblastine and low-dose cyclophosphamide)
• Less than 3 weeks since prior radiation therapy to the site of any progressive lesion that will be identified as a target lesion to measure tumor response

Study design

Design

Study phase:	2
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):	05-10-2012
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Irinotecan
Generic name:	Irinotecan HCl-trihydrate
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Temodal
Generic name:	Temozolomide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Vincristine
Generic name:	Vincristinesulphate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-06-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-10-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-03-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2017

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-04-2019
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	EUCTR2010-023135-42-NL
ISRCTN	ISRCTN66172474
CCMO	NL36401.018.11