PHASE I-II STUDY OF VINBLASTINE IN COMBINATION WITH NILOTINIB IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH REFRACTORY OR RECURRENT LOW-GRADE GLIOMA

Published: 04-09-2013
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Primary:• Phase I part: to define the recommended dose (RD) of nilotinib and vinblastine when used in combination• Phase II part: to evaluate the efficacy of vinblastine in combination with nilotinib (VINILO) at the RD, as compared to vinblastine...

Ethical review	Approved WMO
Status	Pending
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON47673

Source
ToetsingOnline

Brief title
Vinilo

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
low-grade glioma

Research involving
Human

Sponsors and support

Primary sponsor: Gustave Roussy
Source(s) of monetary or material Support: IGR Frankrijk: stichting Imagine for Margot,Novartis

Intervention

Keyword: children, low-grade glioma, nilotinib, phase I/II study

Outcome measures

Primary outcome

Phase I part - Safety assessment

Dose-Limiting Toxicity (DLT), assessed over the first 28-day cycle, defined as

• Grade > 3 neutropenia (<1 x 109/L) for more than 7 days;

• Grade > 2 thrombopenia (<75 x 109/L) or thrombocytopenia requiring

transfusions for more than 7 days.

• Grade 3 or grade 4 non-hematological toxicity, excluding grade 3 nausea,

vomiting, fever, and hepatic toxicity that is rapidly reversible (i.e. returns

to < 2.5 x ULN within 2 weeks after study drug discontinuation), and symptoms

that are related to tumor progression.

and: Any study drug related toxicity occuring during the first cycle leading

to a significant dose reduction considering the 1st cycle

plus the following week (1st week of cycle 2), i.e.:

o If the patient receive less than 80% of the planned

dose of Nilotinib

o If the patient receive less than 75% of the planned

dose of Vinblastine

Phase II part - Efficacy assessment

PFS computed as the time interval between the date of study entry and the date of tumor progression or death (whatever the cause of death). The progression will be defined either radiologically (>25% increase in two-dimension measurements or appearance of new lesions compared to the baseline or to the best response after initiation of therapy) or clinically by new symptoms related to tumor progression (significant decrease of visual acuity, new or worsening neurological deficit). Hydrocephalus is not considered as progression per se.

Secondary outcome

1) Safety monitoring during the treatment

Clinical and laboratory toxicities / symptoms will be graded according to NCI-CTCAE v4.0 over the whole treatment duration. The adverse events which are not reported in the NCI-CTC will be graded as mild, moderate, severe, and life-threatening. In particular, cardiac function will be monitored with echocardiography and ECG.

2) Efficacy criteria

Tumor response will be based on two-dimension measurement and to RANO Criteria (van den Bent, Lancet Oncol 2011). The radiological imaging will be reanalyzed after the study by a radiologist panel, according to the RANO criteria and to the newly defined RAPNO Criteria, once they will be available.

All tumor reduction >25% (CR or PR or MR) will be considered as success.

Morphologic MRI will be performed every 3 months prior to the new cycle, apart from the week 4 early evaluations in case functional MRI is performed. Primary

objective of the study is PFS and thus objective response does not need to be confirmed at 4 to 6 weeks. Baseline MRI and that related to the best response will be centrally reviewed by an independent international radiology panel.

Growth modulation index or progression-free survival time ratio (PFS2/PFS1-ratio), defined as the ratio of a patient*s progression-free survival time from start of study treatment (VINILO or Vinblastine alone), PFS2, relative to the progression-free survival time observed from the patient*s most recent prior anticancer treatment, PFS1, which serves as the patient-specific historical control value.

Modification of functionnal status. In particular, for optic pathway glioma, quantitative assessment of visual acuity and qualitative changes in visual field will be assessed.

Overall survival computed from the date of study entry to the date of death, from any cause.

3) Dose intensity of each drug computed on the whole treatment duration and per month. Duration of treatment and reasons for the end of treatment.

4) Pharmacokinetics dosage of both drugs (for 30 patients of each arm of the phase II part)

5) Functional MRI (perfusion sequence). This dynamic imaging technique will be performed with contrast after 1 month and 3 months of treatment and compared to that performed at study entry. This evaluation will be performed in selected centers (see Appendix 2).

6) Tumor biomarkers will be studied on paraffin tumor samples (histological subtype, vascular density with monoclonal antibody anti-CD105/endoglin,

proliferation index MIB1, immunohistochemical expression of c-kit, PDGFR alpha and beta, and basic protein of myelin or MBP, telomeres length using Q-FISH technique, BRAF status).

7) Pharmacogenetic biomarker (enzyme polymorphism)

8) Long-term follow-up: height, weight, pubertal growth, phosphor-calcic evaluation and cardiac function.

Study description

Background summary

Low grade gliomas (LGG) are the most frequent brain tumor type in children. They are often chemosensitive. However, more than 50% of these tumors will progress within the first 5 years after the start of the treatment and need a second-line therapy (Laithier, JCO 2003). In most cases, patients are still young and the risk of side effects from radiation therapy will call for another medical treatment. If a tumor does not respond to first-line chemotherapy, the prognosis worsens with 25% of deaths within the first 5 years for optic gliomas (de Haas, Pediatr Blood Cancer 2009). Vinblastine (Velbe®) is an effective drug for low grade gliomas with both antiproliferative and antiangiogenic effects. An update of the Canadian phase II of weekly vinblastine (6 mg/m²/week) reported one complete response (CR), three partial responses (PR) and 9 minor responses (MR) in the first 31 patients (Bouffet, JCO, 2012). The 2-year progression-free survival (PFS) rate was 62%. Tolerance of the treatment is fair allowing prolonged maintenance therapy as in Langerhans cell histiocytosis and anaplastic large cell lymphoma (ALCL). These data encourage proceeding with further testing this approach in pediatric low-grade glioma.Nilotinib is a tyrosine kinase inhibitor (TKI) known to affect c-Kit, DDR1 and the PDGF receptors alpha and beta. PDGF is a growth factor for normal and tumoral astrocytes and oligodendrocytes. In addition, PDGF receptors are expressed on pediatric low-grade glioma vessels (McLaughlin, J Pediatr Hematol Oncol 2003; Peyrl, Pediatr Blood Cancer 2009). Tumor response to this class of TKI has been reported occasionally (Peyrl, Pediatr Blood Cancer 2009; McLaughlin, J Pediatr Hematol Oncol 2003). When used as monotherapy, this class of TKI was well tolerated in children, including those with brain tumors (Wayne, Blood 2008; Baruchel, Eur J Cancer 2009; Geoerger, Eur J Cancer 2009).
Taking advantage of their different antiangiogenic mechanisms, their limited and non-overlapping toxicities, vinblastine and nilotinib could play an interesting role in the treatment of pediatric low-grade glioma. Nilotinib via

PDGFRA and c-kit interactions may also interfere with the stroma of the tumor which is a key factor for tumor growth as shown in the NF1 mouse model (Daginakatte, Cancer Res 2008; Kim, Neuroscience 2010; Simmons, J Neuropathol Exp Neurol 2011). Both drugs have also immunostimulating effects especially in dendritic cells, that will be explored during treatment in selected patients (Tanaka, Cancer Res 2009; Nishioka Immunotherapy 2011)
Previous to the phase II assessing the efficacy of the combination compared to vinblastine as single agent, nilotinib and vinblastine have to be administered by escalating dosages in order to identify the recommended doses of each agent when given in combination. This phase I part of the trial is justified by a possible interaction of the two drugs that are substrates of cytochrome P450 CYP3A4. Initial/starting dose of nilotinib (115 mg/m² BID) will be 50% of the recommended dose when used as monotherapy in adults (800 mg/day: 400 mg BID =230 mg/m2 BID). Initial/starting dose of vinblastine will be 50% of the recommended dose when used as monotherapy or in association with other chemotherapeutic drugs (i.e. 3 mg/m2 once a week). This justifies obtaining pharmacokinetic data on both drugs when used in combination. A phase I trial evaluating nilotinib as single agent in pediatrics in hematological malignancies is ongoing, run by the ITCC and the COG group, exploring the dose-levels 230 mg/m² to 460 mg/m² BID. The results of this phase I trial, expected by 2012, and the data of the current trial will be considered to decide whether a higher dose-level for nilotinib can be opened (350 mg/m² BID).

Study objective

Primary:
• Phase I part: to define the recommended dose (RD) of nilotinib and vinblastine when used in combination
• Phase II part: to evaluate the efficacy of vinblastine in combination with nilotinib (VINILO) at the RD, as compared to vinblastine alone, in terms of progression-free survival, in children, adolescents, and young adults with refractory or recurrent low grade glioma and in NF1 patients with low grade glioma at diagnosis.

Secondary:
1. To measure the impact of the VINILO combination compared to vinblastine alone, in terms of tumor response, functionnal status (visual acuity*), progression-free survival time ratio (PFS2/PFS1-ratio), and overall survival (OS)
2. To describe and compare, on the whole duration of treatment, the acute toxicity related to the VINILO combination with that of vinblastine alone; and to compare the long-term effects of both regimens
3. To describe the feasibility of the treatment and the compliance
4. To provide pharmacokinetics data on both drugs when given in combination
5. To identify the predictive value of early functional MRI changes
6. To assess the inter-observers agreement of radiologic response assessment

Exploratory:
1. To explore putative predictors of the response to therapy (tumor, serum and pharmacogenetic biomarkers).

Study design

Multicenter, open label, prospective study including successively a phase I trial and then a phase II trial
Phase I : Open label, non-randomized, sequential dose escalation of both drugs, vinblastine and nilotinib.
Phase II : Open label, randomized study of the combination of nilotinib and vinblastine (VINILO) versus vinblastine alone

Intervention

Phase I part: Nilotinib and Vinblastine dose-escalation
Nilotinib (Tasigna®): 115 to 350 mg/m2 twice daily (BID) orally given continuously (115 mg/m2 once daily if de-escalation requested). The administered dose will be defined for a day, and rounded to the nearest 50 mg dose.
Vinblastine: 3 to 6 mg/m2 once weekly as an IV bolus or in a 15-minute infusion, on Days 1, 8, 15 and 22 of each cycle according to standard practice. Each 28-day cycle is repeated on Day 29/Day 1. No intra-patient dose-escalation is permitted.
Dose allocation will be centrally defined, based on toxicity observed in patients previously evaluated. Every new patient will be treated at the best current recommended dose, i.e. the dose associated with an estimated level of toxicity that is judged acceptable (20% DLT). At least two patients fully observed with no DLT are requested at a given dose level before dose escalation.
Initial dose-escalation scheme
Dose level (DL) Vinblastine weekly Nilotinib
DL-1 3 mg/m2 115 mg/m2 once daily
DL1 (Starting dose) 3 mg/m2 115 mg/m2 BID
DL2 3 mg/m2 230 mg/m2 BID
DL3 4 mg/m2 230 mg/m2 BID
DL4 5 mg/m2 230 mg/m2 BID
DL5 6 mg/m2 230 mg/m2 BID

This scheme is an initial path within the bidimensional space of doses. We will first aim at escaladating the vinblastine dose for a dose of
Nilotinib equal to 230 mg/m² (start-up). However, other adjacent dose combinations to the current dose (excluding the combination with an increase of both agents) can also be explored as soon as DL2 is deemed safe. Thus a combination of Vinblastine 3 mg/m² + Nilotinib
350 mg/m² may be explored as soon as DL2 is deemed safe. The decision to explore the different possible adjacent doses will be basedon the posterior

probability of DLT estimated by the model for all the dose combinations, as well as on the evaluation of the whole safety data, discussed with the Data and Safety Monitoring Board
The phase II part of the study may be opened if the RD of vinblastine is equal or greater than 3 mg/m² and the RD of Nilotinib is equal or greater than 230 mg/m² BID and if the combination is deemed safe. A report describing the phase I results will be sent to the DSMB and the ethics committee. The Phase II part will be opened as a protocol amendment submitted for authorization to the ethics committee and the health authorities.

Phase II part: Patients will be randomly allocated (1:1) to one of the following treatment arms:
A. VINILO-arm: Vinblastine and nilotinib given in combination at the RD defined in the Phase I part:
• Vinblastine: 3 mg/m2 administered as an IV bolus or in a 15-minute infusion as per standard practice, once weekly on Days 1, 8, 15 and 22 of each 28-day cycle.
• Nilotinib (Tasigna®): 230 mg/m2 orally BID given continuously on Days 1-28.
The administered dose will be calculated for a day (460 mg/m²), rounded to the nearest 50 mg dose, and then divided into two doses, with a possible difference of 50 mg between morning and evening uptakes.
Recommended doses of the drug combination will be re-considered at an interim stage of the phase II trial after the analysis of the delayed toxicity encountered in the first 20 patients treated at the initial RD (adaptive design).
B. Control Vinblastine only arm:
• Vinblastine 6 mg/m2 given as an IV bolus or in a 15-minute infusion as per standard practice, once weekly on Days 1, 8, 15 and 22 of each 28-day cycle.
Each 28-day cycle is repeated on Day 29/Day 1.
In both treatment groups, dose reductions and/or administration delays will be performed in case of severe hematological and/or non hematological toxicities while on treatment.
Vinblastine will be temporarily stopped in case of neutropenia <1 x 109/L or thrombopenia <75 x 109/L. It could be re-started at a reduced dose after complete recovery.
Patients benefiting from study treatment may continue up to 12 cycles as long as the toxicity-benefit ratio is adequate.

May 2019: Randomization in the trial is stopped. All patients must be treated according to the current standard, i.e Vinblastine 6 mg/m2 alone.

Study burden and risks

Patients may suffer from regular side-effects such as known for intensive chemotherapy given for malignancies in children, such as hematological toxicity and febrile neutropenia. Nilotinib is known for its potential gastrointestinal

side-effects and skin rash. Vinblastin can cause peripheral neuropathy and constipation. Other not yet known side effects may occur when vinblastin and nilotinib are combined.

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

1. Written informed consent signed by the patient, or parents or legal representative and assent of the minor child where appropriate.
2. Age: 6 months to < 21 years of age at time of study entry;
3. Diagnosis: one of the three conditions listed below

• Refractory or recurrent low-grade glioma after at least one first-line therapy with pathological documentation in non NF1 patients (no further biopsy is needed at study entry)
• Refractory or recurrent low-grade glioma after at least one first-line therapy in NF1 patients, with or without pathological documentation. For patients with NF1 and optic pathway glioma, no biopsy is required to confirm the radiological diagnosis of the low grade glioma.
• Low grade glioma at diagnosis in NF1 patients when the use of chemotherapy is considered for the treatment in case of threat to vision or unequivocal radiological tumor progression. Pathological documentation is advised but not mandatory.
4. Evaluable Disease on morphologic MRI;
5. Karnofsky performance status score >=70% for patients >12 years of age, or Lansky score >=70% for patients <=12 years of age, including patients with motor paresis due to disease.
6. Life expectancy >= 3 months.
7. Administration of stable dose of steroids for at least one week
8. Adequate organ function:
• Adequate hematopoietic function: neutrophils >= 1.0 x 109/L, platelets >= 100 x 109/L; hemoglobin >= 8 g/dL
• Adequate renal function: serum creatinine <= 1.5 x ULN for age. In other cases where serum creatinine >1.5 ULN according to age. Glomerular filtration rate or creatinine clearance has to be
> 70ml/min/1.73m2 or > 70% of the expected value.
• Adequate electrolytes levels: potassium, magnesium, phosphate, total calcium >= Lower Limit of Normal (LLN)
• Adequate hepatic function: total bilirubin <=1.5 x ULN; AST and ALT <=2.5 x ULN.
• Absence of peripheral neuropathy >= grade 2 (Common Toxicity Criteria Adverse Event, NCI CTCAE v4.0)
9. Adequate cardiac function:
• Shortening Fraction (SF) >= 28% (35% for children <3 years) and Left Ventricular Ejection Fraction (LVEF) >= 50% at baseline, as determined by echocardiography;
• Absence of QTc prolongation (QTc QTcF formula) or other clinically significant ventricular or atrial arrhythmia
10. Wash-out period of at least
• 3 weeks in case of preliminary chemotherapy
• 6 weeks in case of nitrosourea-containing chemotherapy
• 2 weeks in the case of treatment with vincristine only
• 6 weeks in case of radiation therapy
11. Possibility of receiving the therapeutic schedule as indicated in the protocol
12. Patients with reproductive potential must use effective/acceptable birth method control (as defined per CTFG guidelines) during their treatment and for up to 90 days after the last dose. Females with reproductive potential must have a negative pregnancy test <= 7 days before randomization.
13. Patients already treated with one of the two drugs can be enrolled in the

trial provided that rechallenging them with the same drug could be considered acceptable

Exclusion criteria

1. Concomitant anti-tumor treatment
2. Not recovered to chemotherapy, immunotherapy or radiotherapy
3. Known intolerance or hypersensitivity to Vinblastine;
4. Existence of another severe systemic disease;
5. Uncontrolled infections not responsive to antibiotics, antiviral medicines, or antifungal medicines
6. Any concurrent illness which in the opinion of the investigator may interfere with the treatment and evaluation of the patient
7. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of nilotinib.
8. Simultaneous treatment with strong cytochromes P450 CYP3A4 inhibitors
9. Simultaneous treatment with antiarrythmic drugs and other drugs known to prolong QT interval
10. Impaired cardiac function including any one of the following
• Clinically significant resting brachycardia
• QTc > 450 msec on baseline ECG. If QTc >450 msec and electrolytes are not within normal ranges, electrolytes should be corrected and then the patient re-screened for QTc.
• Other clinically significant uncontrolled heart disease
• History of or presence of clinically significant ventricular or atrial tachyarrhythmias
11. Positive test for Hepatitis B virus surface antigen

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:	Pending
Start date (anticipated):	01-09-2013
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Tasigna
Generic name:	nilotinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	vinblastine
Generic name:	vinblastine sulphate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	04-09-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-02-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	18-02-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	12-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-07-2019
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-003005-10-NL
ClinicalTrials.gov	NCT01884922(fase1)&NCT01887522(fase2)
CCMO	NL42257.078.13

Study results

Results posted: 21-11-2022

First publication
10-11-2022