Vincristine and concomitant azole therapy in pediatric acute lymphoblastic leukemia patients - a pharmacokinetic study

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Primary objective:To assess vincristine pharmacokinetics during concomitant azole therapy, which is given in the context of standard treatment (hence this concerns an observational and not an intervention study)Secondary objectives:- To evaluate the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Observational invasive

Summary

ID

NL-OMON35826

Source
ToetsingOnline

Brief title
VCR-Azole study

Condition

- Leukaemias

Synonym
Acute lymphoblastic leukemia - cancer of white blood cells

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Stichting Go4Children

Intervention

Keyword: Acute lymphoblastic leukemia, Azole therapy, Pharmacokinetics, Vincristine

Outcome measures

Primary outcome

Blood levels of vincristine and the metabolite, M1 will be analyzed after administration of vincristine.

Secondary outcome

Blood levels of the azoles will be analyzed at the same time. One whole blood sample for DNA extraction and genotyping will be collected from each patient enrolled in this study. Furthermore, we will study toxicity.

Study description

Background summary

Vincristine (VCR) is an important component in the treatment of acute lymphoblastic leukemia (ALL) in children. Proper dosing of vincristine is required to maximize disease control while avoiding toxicity. Peripheral and autonomic neuropathies are the most common side effects which can be life-threatening. Vincristine pharmacokinetics are time- and dose-dependent and considerable intra- and interpatient variation have previously been reported. Vincristine is predominantly metabolized in the liver by the cytochrome P450 (CYP) 3A family of enzymes and eliminated by an efflux pump, P-glycoprotein (P-gp). Inhibition of CYP3A4 by several drugs, such as azole antifungals, could increase vincristine exposure and potentiate the side effects caused by vincristine. Since in paediatric oncology patients azoles are increasingly being used for prophylaxis and treatment of fungal infections, guidelines for the co-administration of vincristine and azole therapy are necessary. The azoles used for antifungal prophylaxis are itraconazole, voriconazole and fluconazole. Several case reports suggest that co-administration of azoles and vincristine lead to increased toxicity, but this has not been studied specifically. It is not known whether these side-effects are related to a higher exposure of vincristine, and to what extent this exposure is increased.

Information of the increase in plasma levels of vincristine during concomitant azole therapy may lead to evidence-based dosing guidelines for the effective and safe co-administration of these drugs, assuming that lower dose-levels of vincristine are needed.

Study objective

Primary objective:

To assess vincristine pharmacokinetics during concomitant azole therapy, which is given in the context of standard treatment (hence this concerns an observational and not an intervention study)

Secondary objectives:

- To evaluate the (neuro) toxicity of the combination of vincristine and azole therapy in relation to the pharmacokinetics of both vincristine and azole
- To evaluate the (genetic) factors contributing to intrapatient variability in vincristine pharmacokinetics and dynamics (e.g. toxicity)

Study design

A prospective, non-randomised multicentre study will be performed with patients treated at the Pediatric Oncology departments of the Emma Childrens* Hospital in Amsterdam, the Erasmus MC- Sophia Childrens* Hospital Rotterdam and the Radboud University in Nijmegen for treatment for acute lymphoblastic leukemia (ALL). The patients will be enrolled either on treatment with vincristine or on treatment with vincristine and concomitant azole therapy. The study will take place during Induction phase or Intensification phase for MR patients in the DCOG-ALL protocol. To study the effect of the concomitant azole therapy on the pharmacokinetics of vincristine a population based pharmacokinetic model will be used.

Study burden and risks

Extra blood sampling in pediatric oncology patients gives minimal burden, since regular blood sampling is obtained during the treatment process for ALL patients. Blood sampling will be done using the existing vascular access ports and the volume of blood will be 10 x 2.5 ml, 1 x 5 ml and 8 x 0.5 ml. Manipulation of the vascular port will minimally increase the risk of infection. The study needs to be performed in pediatric patients since ALL is most common in this population and during the treatment of ALL concomitant azole prophylaxe is used in the prevention of systemic infections during neutropenia.

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

- Diagnosed with acute lymphoblastic leukemia
- Treatment according to nationwide DCOG ALL protocol, induction therapy and/or intensification therapy for Medium Risk Group patients
- Vincristine 1.5 mg/m2 or 2 mg/m2 as iv bolus according to nationwide ALL protocol
- Age 1 - < 18 years
- Azole group: standard azole prophylaxis according to institutional guidelines (itraconazole, voricoanzole therapy started at least 5 days before planned vincristine sampling, fluconazole 7 days)
- Written informed consent from patients or from parents or legal guardians for minor patients, according to local law and regulations

Exclusion criteria

- Blood sampling not possible
- Patient refusal or parent refusal
- Not able to comply with scheduled follow-up
- Patients with underlying neurological disease such as Charcot-Marie-Tooth disease or Guillain-Barre syndrome
- Patients with underlying Down syndrome

Study design

Design

Study phase:	4
Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-02-2012
Enrollment:	40
Type:	Actual

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
CCMO	NL36660.018.11