A Phase I/II study of Azacitidine (Vidaza®) in pediatric patients with relapsed high-grade pediatric MDS or JMML.

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20806

Source
NTR

Brief title
Vidaza study in pediatric MDS and JMML

Health condition

- Pediatric myelodysplatsic syndrome (MDS)
-Juvenile myelomonocytic leukemia (JMML)

Sponsors and support

Primary sponsor: Erasmus MC, Rotterdam, The Netherlands
Source(s) of monetary or material Support: Celgene corporation, Stichting Go4Children

Intervention

Outcome measures

Primary outcome

The current study aims to establish the recommended dose, safety and preliminary efficacy of azacitidine administered IV in children with advanced newly diagnosed or relapsed/refractory MDS or JMML, in 4 different subgroups (strata) of patients. Recommended dose will be determined by:

1. Dose-limiting toxicities;

2. DLTs are AEs considered at least possibly drug-related and will be limited to the first course of azacitidine.

Secondary outcome

1. To determine the safety and tolerability of azacitidine per stratum;

2. To determine (preliminary) the hematological remission rate in these patients;

3. To describe the durability of response and long-term follow-up, including that of patients undergoing stem-cell transplant after treatment with azacitidine;

4. To determine the plasma pharmacokinetic parameters of azacitidine;

5. To study the pharmacodynamic effects of azacitidine in pediatric MDS and JMML.

Efficacy will be determined by response definitions:

1. For advanced MDS: Cheson et al, 2006;

2. For JMML :Chan et al, 2009.

Study description

Background summary

This is an international, collaborative, prospective, open label, phase I/II trial to establish the recommended dose and preliminary efficacy of azacitidine in children with relapsed high-grade MDS or JMML. Myelodysplastic syndromes (MDS) and juvenile myelomonocytic leukemia (JMML) are rare malignant diseases of childhood. So far, stem cell transplantation is the only curative treatment option. No other agents are available to treat these diseases successfully, and HSCT results in approximately 50% survival only; hence there is clear unmet medical need. Over the past few years, we have increasing evidence that aberrant methylation contributes to the malignant phenotype of JMML and childhood advanced MDS. The demethylating agent azacitidine has been shown to improve survival in adults with MDS,

but so far no studies are available in children with MDS or JMML. In the current study we want to establish the recommended dose and preliminary efficacy of azacitidine, in children with relapsed MDS or JMML in a pre-transplantation window. This study will provide a preliminary proof of concept whether a demethylating agent is able to induce responses in these diseases, and whether this agent indeed results in hypomethylation. Pharmacodynamic studies should provide this proof of concept. It needs to be mentioned that the HSCT procedure itself is not part of this protocol and should be performed under EWOG or institutional guidelines at the discretion of the principle investigator.

Two dose-levels will be studied:

1. Level 1: 75 mg/m2/day IV x 7 days with a 28-day interval;

2. Level 2: 100 mg/m2/day IV x 7 days with a 28-day interval.

In this study 2 subgroups of patients are eligible, which will be enrolled in 2 different strata:

1. Stratum 1: Relapsed patients with MDS in a ‘re-transplantation window’. At relapse azacitidine may also be continued when a 2nd transplant is not feasible, as long as the patient benefits from treatment;

2. Stratum 2: Relapsed patients with JMML in a ‘re-transplantation window’. Azacitidine may also be continued when a 2nd transplant is not feasible and as long as the patient benefits from treatment.

The patients in the two strata need to be analyzed separately as there may be marked differences in tolerability and response.

For the MDS arm, if there is at least one patient achieving response (defined as CR or PR) and there
are no patients experiencing a dose-limiting toxicity among the three first patients in stage one,
another three patients will be treated at the next higher dose level, if applicable. In case of 1 dose-
limiting toxicity among the first three patients, the cohort will be expanded to 6 patients at the
starting dose-level. If there is at least one out of six patients achieving response and no more than
one patient experiences a dose-limiting toxicity in stage one, stage two shall open for enrolment. In

case of no responses the arm shall be closed to enrollment. In case there is more than one dose-
limiting toxicity in stage one, the dose is set to the previous level (if applicable), and stage 2 shall
open for enrolment if at least one patient responded at that dose-level. Otherwise, the arm shall be
closed to enrolment.

The dose will be increased only if <2 of the 6 evaluable patients (30%, across stage-one and stage-
two) achieve a response, and/or there are ≤ two dose-limiting toxicities; otherwise the therapy will
be deemed unpromising for further consideration.

For the JMML arm, the safety run-in will include 3 patients and the tolerability of the therapy will be
considered using a classic 3+3 design. Should the therapy be considered tolerable, stage one shall
enrol patients to a higher dose, or otherwise the patients in the safety run-in will be considered part
of stage one. During stage-one, if ≥ 1 of the 3 evaluable patients for the primary endpoint achieve a
response then stage two shall open to enrolment, or otherwise that arm shall be closed to
enrolment. At the end of stage two, the therapy will be considered positive for possible further
investigation if ≥ 2 of the 6 evaluable patients (30%, across stage-one and stage-two) achieve a
response; or otherwise considered unpromising for further consideration.

We will recruit a maximum of 12 patients in each stratum, and hence 24 patients in total. Including
screen failures or drop-outs or in case of DLTs we may need to recruit a maximum of 28 patients.

The study will last approximately 8 years from first patient first visit (FPFV) to last patient last visit (LPLV).

Study objective

There is clear medical need in pediatric high-grade MDS and JMML to control disease pre-SCT without the disadvantages associated with intensive chemotherapy. So far no agents have been successfully applied in this window, or are specifically registered for use in these

disease conditions.

Based on adult data in MDS using the hypomethylating agent azacitidine regarding efficacy, and the favorable safety profile, we feel that a study in pediatric MDS is warranted. There are unpublished data suggesting that hypermethylation is also an important mechanism of disease pathogenesis in JMML, which is a subentity of pediatric MDS.

There are available pediatric safety data using azacitidine dosages that are much higher than proposed in this study, therefore we decided not to dose-reduce azacitidine in this study but to use a similar dose as has been shown to be safe and effective in adult MDS. Apparently this dose results in adequate hypomethylation, whereas the leukemia studies in the past have focused on the use of azacitidine as a regular cytotoxic compound (hence MTD-based).

We aim at determining a recommended dose for pediatric MDS and JMML and provide preliminary efficacy data, as well as pharmacokinetics and dynamics.

Study design

Response and safety will be evaluated at differen time-points according to the stratum the patient is included is. DLTs are limited to the 1st course of treatment.

28-nov-2018: Inclusion stratum 1 (relapsed MDS) closed.

Intervention

Vidaza will be given IV for 7 days with a 28-day interval.

In this study 2 subgroups of pediatric MDS and JMML patients are eligible, and will be enrolled in 2 different strata:

1. Stratum 1: Relapsed patients with MDS in a ‘re-transplantation window’. At relapse azacitidine may also be continued when a 2nd transplant is not feasible, as long as the patient benefits from treatment;

2. Stratum 2: Relapsed patients with JMML in a ‘re-transplantation window’. Azacitidine may also be continued when a 2nd transplant is not feasible and as long as the patient benefits from treatment.

Contacts

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Eligibility criteria

Inclusion criteria

1. Established diagnosis of relapsed MDS or JMML according to EWOG-criteria, after a prior stem cell transplantation;

2. 1 month to ≤ 18 years old;

3. Lansky play score > 60; or Karnofsky performance status > 60;

4. Life expectancy ≥ 3 months;

5. Normal renal function defined as less than or equal to NCI-CTCAE grade 1 (max 1.5 x ULN);

6. Normal liver function defined as less than or equal to NCI-CTCAE grade 1 (max 2.5 x ULN for transaminases and bilirubin);

7. No other chemotherapy within 3 weeks of start of study medication; For 6-MP or low-dose cytarabine in JMML patients 1 week wash-out time is sufficient.

8. For JMML patients: no oxygen need due to pulmonary infiltration and saturation >92% without need for oxygen therapy;

9. For JMML patients: peripheral blood monocyte count > 1.0x109/l

10. For relapsed patients: minimum 3 months following stem cell transplantation, and recovery of all acute toxic effects of prior chemotherapy/stem-cell transplantation;

11. Able to comply with scheduled follow-up and with management of toxicity;

12. Reproductive Function

• Female patients of childbearing potential must have a negative urine or serum pregnancy test
confirmed prior to enrollment.

• Female patients with infants must agree not to breastfeed their infants while on this study.

• Male and female patients of child-bearing potential must agree to use an highly effective method
of contraception approved by the investigator during the study and for 90 days after the last dose of
azacitidine.

• Highly effective methods of contraception include (but not exclusively) the following contraceptive
methodsFor patients with childbearing potential, a negative pregnancy test should be available;

13. Written informed consent from patients or from parents or legal guardians for minor patients,
according to local law and regulations

Exclusion criteria

1. Prior or current history:

o Other serious illnesses or medical conditions

o Genetic abnormalities indicative of AML

2. JMML patients in whom a diagnosis of Noonan syndrome is suspected based on clinical history
and/or presenting symptoms

3. Patients with secondary MDS with underlying bone-marrow failure syndromes or with familial
MDS

4. Isolated extramedullary disease

5. Symptomatic CNS-involvement

6. Current uncontrolled infection

7. Cardiac toxicity (shortening fraction below 28%)

8. Concurrent treatment with any other anti-cancer therapy is not allowed

9. Pregnant or lactating patients

10. Patients who cannot be regularly followed up for psychological, social, familial or geographic
reasons

11. Patient with expected non-compliance to toxicity management guidelines

12. Prior treatment with a demethylating agent

13. Allergy to azacitidine or mannitol.<

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL
Recruitment status:	Recruitment stopped
Start date (anticipated):	01-01-2011
Enrollment:	60
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	25-10-2010
Application type:	First submission

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
NTR-new	NL2461
NTR-old	NTR2578
Other	Consortium Innovative Therapy for Children with Cancer : ITCC-015
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A