

Phase II study of combination therapy with 5-AZAcytidine, Valproic acid, and All-Trans Retinoic Acid in patients with myelodysplastic syndromes and other myeloid malignancies who cannot receive intensive chemotherapy

Submission date 28/03/2007	Recruitment status No longer recruiting	☐ Prospectively registered ☐ Protocol
Registration date 19/07/2007	Overall study status Completed	☐ Statistical analysis plan ☒ Results
Last Edited 28/10/2021	Condition category Cancer	☐ Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2005-004454-27

Protocol serial number
AZAVATRA_V01

Study information

Scientific Title

Phase II study of combination therapy with 5-AZAcytidine, Valproic acid, and All-Trans Retinoic Acid in patients with myelodysplastic syndromes and other myeloid malignancies who cannot receive intensive chemotherapy

Acronym

AZAVATRA

Study objectives

Myelodysplastic Syndromes (MDS) are acquired clonal bone marrow disorders, characterised by impaired maturation and dysplastic morphology of haematopoietic precursor cells. Patients with MDS suffer from ineffective haematopoiesis, causing anaemia, infectious complications, and haemorrhagic diathesis. Leukaemic transformation occurs in about 25% of cases.

In vitro studies suggest that combining two principles of epigenetic treatment, namely reversal of Deoxyribonucleic Acid (DNA) promoter hypermethylation by inhibitors of DNA methyltransferases, and reversal of chromatin condensation by histone acetylase inhibitors, synergize in reversing abnormal gene silencing.

The principal question of this clinical trial is to test whether the in vitro findings can be translated into therapeutic success in vivo.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Approval received from the Ethics Committee of the medical faculty of the Heinrich-Heine-University (leading) and the Ethics Committee of medical faculty of the Johann-Wolfgang-Goethe University on the 22nd June 2006 (ref: MC-LKP-107).

Primary study design

Interventional

Study design

Phase II, open, prospective, single-armed, multicentre trial.

Study type(s)

Treatment

Health condition(s) or problem(s) studied

Myelodysplastic syndromes (MDS)

Interventions

Epigenetic treatment of MDS with demethylating agents has achieved remarkable clinical responses and seems to be superior to supportive care or intensive chemotherapy. Low-dose 5-azacytidine was the first drug shown to alter the natural course of MDS by significantly prolonging the time until leukaemia transformation.

At our institute we tried a different type of epigenetic treatment when we conducted the first clinical trial with Valproic Acid (VPA) in MDS. This drug has been shown to act as an inhibitor of Histone Deacetylase (HDAC). Since HDAC inhibitors and demethylating agents show synergistic effects in vitro, it appears promising to try the combination in vivo.

The differentiation-inducing agent All-Trans Retinoic Acid (ATRA) will be added after four months if 5-Aza plus VPA do not produce a satisfactory treatment response.

The treatment was as follows:

1. From beginning: Valproic acid 1500 - 2000 mg/d over one year, and azacytidine 100 mg/m²/d applied over five days repeated every 28 days
2. After four months (if no improvement): All-trans retinoic acid 80 mg/m²/d day one to seven repeated every 14 days

Intervention Type

Drug

Phase

Phase II

Drug/device/biological/vaccine name(s)

5-Azacytidine (5-Aza), Valproic Acid (VPA), and All-Trans Retinoic Acid (ATRA)

Primary outcome(s)

Safety/toxicity, assessed at one year after treatment start.

Key secondary outcome(s)

All endpoints will be assessed at one year after treatment start:

1. Haematological response
2. Progression-free survival
3. Overall survival

Completion date

01/05/2010

Eligibility

Key inclusion criteria

1. Primary Myelodysplastic Syndromes (pMDS) with unfavourable risk profile (more than 10% blast cells in the bone marrow, unfavourable karyotype)
2. Therapy-related (secondary) Myelodysplastic Syndromes (sMDS)
3. Chronic Myelomonocytic Leukaemia (CMML)
4. De-novo or secondary acute myeloid leukemia in elderly patients who cannot be treated with intensive chemotherapy

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Not Specified

Sex

Not Specified

Total final enrolment

24

Key exclusion criteria

1. Impaired liver or kidney function
2. Pregnancy
3. Simultaneous participation in another clinical trial

Date of first enrolment

19/03/2007

Date of final enrolment

01/05/2010

Locations

Countries of recruitment

Germany

Study participating centre

Department of Haematology, Oncology and Clinical Immunology

Duesseldorf

Germany

40225

Sponsor information

Organisation

Heinrich-Heine-University (Germany)

ROR

<https://ror.org/024z2rq82>

Funder(s)

Funder type

University/education

Funder Name

Heinrich-Heine-University (Germany)

Results and Publications

Individual participant data (IPD) sharing plan

Not provided at time of registration

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		05/02/2020	28/10/2021	No	No