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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 [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 19/07/2007	**Overall study status** Completed	
Last Edited 28/10/2021	**Condition category** Cancer	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2005-004454-27

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
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 haematopoesis, 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).

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

Primary study design
Interventional

Secondary study design
Multi-centre

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

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/m^2/d applied over five days repeated every 28 days
2. After four months (if no improvement): All-trans retinoic acid 80 mg/m^2/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 measure
Safety/toxicity, assessed at one year after treatment start.

Secondary outcome measures
All endpoints will be assessed at one year after treatment start:
1. Haematological response
2. Progression-free survival
3. Overall survival

Overall study start date
19/03/2007

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

Age group
Not Specified

Sex
Not Specified

Target number of participants
25

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
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Sponsor information

Organisation
Heinrich-Heine-University (Germany)

Sponsor details
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Sponsor type
University/education

Website
http://www.uni-duesseldorf.de/

ROR
https://ror.org/024z2rq82

Funder(s)

Funder type
University/education

Funder Name
Heinrich-Heine-University (Germany)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

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