THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

Randomized controlled study of post-transplant azacitidine for prevention of acute myelogenous leukemia and myelodysplastic syndrome relapse (VZ-AML-PI-0129)
2008-0503

Core Protocol Information

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Full Title:	Randomized controlled study of post-transplant azacitidine for prevention of acute myelogenous leukemia and myelodysplastic syndrome relapse (VZ-AML-PI-0129)
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Abstract

Objectives:

Primary

1. To compare in a randomized controlled fashion the relapse-free survival of acute myelogenous leukemia and myelodysplastic patients treated with post transplant maintenance azacitidine.

Secondary

1. To compare survival of patients receiving azacitidine with that of untreated controls.
2. To document toxicity of maintenance therapy with azacitidine.

Rationale: (Be as concise as possible)

Allogeneic hematopoietic stem cell transplantation for patients with high-risk acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) is associated with high failure rates. Although this form of treatment is associated with a high complete remission rate, the major cause of failure is disease relapse, which usually occurs early after transplantation.

Here we propose to use maintenance treatment with low doses of 5-azacitidine (Vidaza) after transplantation. The rationale for the choice of low doses of azacitidine is as follows: recovering marrows after transplantation are very susceptible to myelosupression, and higher doses are not well tolerated; in addition, we are not seeking a cytotoxic effect, but hope to induce hypomethylation and myeloid cell differentiation and possibly, magnify the graft-versus-leukemia effect. We have defined the safety of a dose at 32 mg/m2 for 5 days, repeated at 28 day cycles, and now plan to evaluate this maintenance strategy in a randomized, controlled fashion.

Eligibility: (List All Criteria)

Inclusion:

1) Patients with a diagnosis of AML (World Health Organization classification: >=20% blasts in the bone marrow and / or peripheral blood) or MDS (International Prognostic Scoring System intermediate-1 or higher) that at the time of allogeneic transplantation were in: - Induction Failure, relapsed disease or second or greater remission; patients in first complete remission that required more than 1 cycle of treatment to achieve the remission, or that have AML evolving from MDS, or that had the following abnormalities: FLT3 mutation, deletion of chromosome 5 or 7, MLL gene rearrangement, or more than or equal to 3 cytogenetics abnormalities. Patients with de novo or therapy-related MDS, CMML, or AML are also eligible, regardless of cytogenetics or molecular rearrangements.

2) Biphenotypic Leukemia that at the time of allogeneic transplantation was in induction failure, relapsed disease, first, second or greater remission.

3) Patients must be in complete remission post transplant.

4) Patient may be enrolled 40 to 100 days after transplant.

5) Age 18 to 75 years old.

6) Serum creatinine < 1.8 mg/dL or creatinine clearance greater or equal than 40 cc/min as defined by the Cockcroft-Gault Equation*. a. Males(mL/min):(140-age)*IBW(kg) / 72*(serum creatinine(mg/dl)) b. Females(mL/min):0.85*(140-age)*IBW(kg) / 72*(serum creatinine(mg/dl)).

7) Serum direct bilirubin < 1.5 mg/dL (unless Gilbert's syndrome).

8) SGPT </= 200 IU/ml unless related to patient's malignancy.

9) Be able to understand and sign informed consent.

Exclusion:

1) Active uncontrolled infection.

2) Presence of uncontrolled graft-versus-host disease.

3) Patients that underwent allogeneic transplantation as a treatment of graft failure.

4) Pregnancy or breast-feeding (women of childbearing potential, any female who has experienced menarche and who has not undergone surgical sterilization or is not post-menopausal with a positive serum pregnancy test.

5) Known or suspected hypersensitivity to azacitiadine or mannitol.

6) Patients with advanced malignant hepatic tumors.

Is there an age limit? Yes

Why? Provide scientific justification:
The upper limit (75 years) is determined by physiologic limitations. The lower limit is dictated by the small numbers of patients that have the diseases studied here, a fact that prevents meaningful conclusions in the pediatric population.

Disease Group:

Leukemia

Treatment Agents/Devices/Interventions:

Azacitidine

Proposed Treatment/Study Plan:

Standard treatment post allogeneic transplant is supportive care only.

Statistical Considerations:

Preliminaries

This is a randomized, controlled phase III trial to compare azacitidine (AZA) maintenance to standard of care in patients with high risk AML/MDS who have undergone an allogeneic stem cell transplant (allotx). Patients will be randomized fairly between azacitidine and standard of care. Starting at 40 to 100 days post allotx, patients randomized to the azacitidine arm will receive 32 mg/m2 for five consecutive days of each 28 day cycle and the maximum treatment will be 12 cycles. Each cycle will consist of approximately 28 days, allowing the possibility that treatment within a cycle may be delayed for up to 4 weeks due to organ toxicity or hematologic toxicity.

Group sequential design

The primary outcome for treatment evaluation will be relapse-free survival (RFS) time. A null historical RFS time of 6 months will be assumed. The goal will be to

test the hypothesis that azacitidine provides at least a 50% improvement in m = median RFS, from 6 to 9 months. An accrual rate of 6 patients per month will be assumed. A two-sided group sequential procedure will be used [2] with overall type I error .05 and power .80 to detect the alternative m = 9 months, with up to 2 interim tests and one final test, including both outer bounds for superiority and inner bounds for futility. All tests will be based on a standardized log rank statistic, and will be performed using the following cut-offs.

No. Events	Outer Z-score cut-off to reject the null hypothesis (Superiority)	Inner Z-score cut-off to accept the null hypothesis (Futility)
71	+/- 3.7103	+/- .2438
142	+/- 2.5114	+/- 1.0268
214	+/- 1.993	+/- 1.993

The number of patients accrued (sample size) required to achieve the necessary numbers of events required by the group sequential tests will be between 213 and 246 (all to be enrolled at MDACC).

The randomization will be stratified by disease (AML, MDS, biphenotypic leukemia).

Secondary outcomes

Additional outcomes that will be recorded and analyzed will include overall survival (OS) time, acute (grade 3 or 4) graft-versus host disease, organ toxicity and hematologic toxicity.

Data analyses

All adverse events will be cross-tabulated with treatment arm, and the rates compared using a Fisher exact test. Unadjusted RFS and OS times will be estimated using the Kaplan-Meier method. Covariate adjusted comparisons will be done using a Cox model or other appropriate time-to-event regression model to be determined by preliminary goodness-of-fit analyses.

Where Will Participants Be Enrolled:

Only at MDACC

Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)? No

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? No

Estimated Accrual:

Total Accrual at MDACC: 246
Estimated monthly accrual at MDACC: 6

Accrual Comments:

Do you expect your target population to include non-english speaking participants? No

Location of Treatment:

This protocol is performed on an Outpatient basis.

Length of Stay: What is the length & frequency of hospitalization?

No hospitalization is planned under this study.

Return Visits: How often must participants come to MDACC?

Daily for 5 days of each 28 day-cycle (for drug administration). Once prior to starting the drug and once weekly for 2 weeks after drug administration is completed for labs. Pts are to receive azacitidine for no more than 1 year after the first dose.

Home Care: Specify what, if any, treatment may be given at home.

There is no home care under this study. However, local physicians, should they agree to administer the drug as prescribed here, will administer azacitidine.

Name of Person at MDACC Responsible for Data Management: Jennifer D. Ramos

Prior protocol at M. D. Anderson:

Has the Principal Investigator ever had a clinical or behavioral protocol at MDACC that accrued patients? Yes

Data Monitoring Committee:

Is treatment assignment randomized? Yes

Is this a blinded or double-blinded study? No

Does this Protocol need data safety monitoring? Yes

Provide the name of the data safety monitoring board (DSMB) monitoring this protocol:
MDACC DMC

Does this protocol have a schedule for interim and final analysis? Yes

Please describe:

We plan to have interim analyses when accrual reaches 71 and 142 patients, and a final analysis when we complete enrollment, as described in the statistical section.

Radiation Safety:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent?	No
Is the radioactive compound (or drug) FDA approved and/or commercially available?	No

Investigational New Drugs:

Does this protocol require an IND? No

☒ **Please confirm that the protocol meets all criteria for exemption according to 21CFR 312.2(b), noted below:**

(b) Exemptions. (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of 312.7.

Rationale for Exemption:
Please include a detailed rationale as to why this drug should be considered exempt from FDA IND regulations, including any available references to the prior use of the regimen or drug combination in human subjects.

We are completing study 2005-0417, which determined the dose and schedule of azacitidine given after allogeneic transplant. That protocol did not require an IND. Here we plan to determine the efficacy of this approach, using the dose determined in the previous study, and therefore believe that we do not need an IND.

If this protocol includes an FDA Approved Therapy, please list the disease, dose and route of administration:

	Approved Use	Proposed in this Protocol
Disease:	MDS	AML/MDS
Dose:	75 mg/m2 X 7 days	32 mg/m2 X 5 days
Route of Administration:	SQ	SQ

Investigational Device:

Is the Investigational Device approved by the FDA? N/A

Is the Investigational Device being used in the manner approved by the FDA? N/A

Has the Investigational Device been modified in a manner not approved by the FDA? N/A

Name of Device:

Manufacturer:

What is the FDA Status of the Investigational Device?

Is the study being conducted under an Investigational Device Exemption (IDE)? No

IDE Holder:

IDE Number:

Risk Assessment:
Please answer the following questions regarding the Investigational Device.

Intended as an implant? No

Purported or represented to be for use supporting or sustaining human life? No

For use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health? No

You may attach sponsor documentation of the risk assessment:

Will participant be charged for the Investigational Device?

Sponsorship and Support Information:

Does the Study have a Sponsor or Supporter? Yes

Sponsor or Supporter: Celgene
Type(s) of Support: Agent

Monitored by Sponsor or Sponsor Represenative (CRO)? No

Is this Protocol listed on any Federal Grant or Foundation Funding Application? No

Biosafety:
Does this study involve the use of Recombinant DNA Technology? No

Does this study involve the use of organisms that are infectious to humans? No

Does this study involve stem cells? No

Technology Commercialization:

Does this study include any agents or devices manufactured or produced at MD Anderson Cancer Center? No

Laboratory Tests:

Where will laboratory tests be performed on patient materials? (Please select all that apply)
Other
Please provide the name of the test(s), the purpose of the test, and the performing laboratory identification and contact information.

Dr. Katy Rezvani's laboratory and Dr. Simrit Parmar's laboratory at MD Anderson will receive samples to study immune recovery after allogeneic transplant. Dr. Garcia-Manero's laboratory and Dr. Simrit Parmar's laboratory at MD Anderson will receive samples for methylation studies.

Manufacturing:

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study? No