Daunorubicin, Cytarabine, and Midostaurin in Treating Patients With Newly Diagnosed Acute Myeloid Leukemia

ClinicalTrials.gov Identifier: NCT00651261

Recruitment Status: Active, not recruiting
First Posted: April 2, 2008
Results First Posted: February 6, 2017
Last Update Posted: May 8, 2018

Sponsor:
Alliance for Clinical Trials in Oncology

Collaborators:
National Cancer Institute (NCI)
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Alliance for Clinical Trials in Oncology

Study Description

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Brief Summary:
The purpose of this study is to compare the effects, good and/or bad, of a standard chemotherapy regimen for AML that includes the drugs daunorubicin and cytarabine combined with or without midostaurin (also known as PKC412), to find out which is better. This research is being done because it is unknown whether the addition of midostaurin to chemotherapy treatment is better than chemotherapy treatment alone. Midostaurin has been tested in over 400 patients and is being studied in a number of illnesses, including AML, colon cancer, and lung cancer. Midostaurin blocks an enzyme, produced by a gene known as FLT3, that may have a role in the survival and growth of AML cells. Not all leukemia cells will have the abnormal FLT3 gene. This study will focus only on patients with leukemia cells with the abnormal FLT3 gene.

Condition or disease	Intervention/treatment	Phase
Leukemia	Drug: cytarabine Drug: daunorubicin Drug: midostaurin Other: placebo Drug: dexamethasone acetate	Phase 3

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Study Design

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Study Type:	Interventional (Clinical Trial)
Actual Enrollment:	717 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Double (Participant, Investigator)
Primary Purpose:	Treatment
Official Title:	A Phase III Randomized, Double-Blind Study of Induction (Daunorubicin/Cytarabine) and Consolidation (High-Dose Cytarabine) Chemotherapy + Midostaurin (PKC412) (IND #101261) or Placebo in Newly Diagnosed Patients < 60 Years of Age With FLT3 Mutated Acute Myeloid Leukemia (AML)
Study Start Date:	April 2008
Actual Primary Completion Date:	July 2016

Resource links provided by the National Library of Medicine

Genetics Home Reference related topics:
- Core binding factor acute myeloid leukemia
- Cytogenetically normal acute myeloid leukemia
- Familial acute myeloid leukemia with mutated CEBPA

MedlinePlus related topics: Acute Myeloid Leukemia Leukemia

Drug Information available for: Cytarabine Daunorubicin Daunorubicin hydrochloride Midostaurin

Genetic and Rare Diseases Information Center resources:
- Myeloid Leukemia Acute Myeloid Leukemia
- Acute Non Lymphoblastic Leukemia
- Acute Lymphoblastic Leukemia
- Acute Myeloblastic Leukemia Without Maturation
- Acute Myeloblastic Leukemia With Maturation
- Acute Erythroid Leukemia Acute Megakaryoblastic Leukemia
- Acute Myelomonocytic Leukemia Di Guglielmo's Syndrome
- Acute Monoblastic Leukemia

U.S. FDA Resources

Arms and Interventions

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Arm	Intervention/treatment
Experimental: Induction and consolidation chemotherapy plus midostaurin Patients will receive a standard combination of chemotherapy drugs during remission induction therapy that includes cytarabine, daunorubicin, and the experimental drug midostaurin. Depending on the outcome of remission induction treatment, there may	Drug: cytarabine Given IV Drug: daunorubicin

be a decision to discontinue the study treatment or a second remission induction cycle may be given. If remission induction therapy is successfully completed, patients will receive four courses of high-dose cytarabine consolidation chemotherapy plus dexamethasone together with the experimental drug midostaurin. All patients will undergo a bone marrow aspiration (and perhaps a biopsy) after the final course of remission consolidation chemotherapy. If the patient continues to respond to the treatment, the patient will receive continuation therapy with midostaurin for twelve (12) months.	Given IV Drug: midostaurin Given orally Drug: dexamethasone acetate ocular medication administration
Active Comparator: Induction and consolidation chemotherapy plus placebo Patients will receive a standard combination of chemotherapy drugs during remission induction therapy that includes cytarabine, daunorubicin, and placebo. Depending on the outcome of remission induction treatment, there may be a decision to discontinue the study treatment or a second remission induction cycle may be given. If remission induction therapy is successfully completed, patients will receive four courses of high-dose cytarabine consolidation chemotherapy plus dexamethasone together with placebo. All patients will undergo a bone marrow aspiration (and perhaps a biopsy) after the final course of remission consolidation chemotherapy. If the patient continues to respond to the treatment, the patient will receive continuation therapy with placebo for twelve (12) months.	Drug: cytarabine Given IV Drug: daunorubicin Given IV Other: placebo Given orally Drug: dexamethasone acetate ocular medication administration

Outcome Measures

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Primary Outcome Measures :

1. Overall Survival (OS) [Time Frame: Duration of study (Up to 10 years)]

   Overall survival (OS) was defined as the time interval from randomization to death from any cause. The median OS with 95% CI was estimated using the Kaplan-Meier method.

Secondary Outcome Measures :

1. Event- Free Survival [Time Frame: Duration of study (Up to 10 years)]

   Event free survival (EFS) was defined as the time from randomization until the earliest qualifying event, including: failure to obtain a CR on or before 60 days of initiation of protocol therapy; relapse; or death from any cause. Patients alive and event free at the time of analysis were censored on the date of last clinical assessment. The median EFS with 95% CI was estimated using the Kaplan-Meier method.

   Due to a higher than expected transplant rate, EFS was promoted to be a key secondary endpoint.

2. Overall Survival, Censoring Participants Who Receive a Stem Cell Transplant at the Time of the Transplant [Time Frame: Duration of study (Up to 10 years)]

   Overall survival (OS) was defined as the time interval from randomization to death from any cause. Any participants who received a stem cell transplant were censored at the time of transplant. The median OS with 95% CI was estimated using the Kaplan-Meier method.

3. Complete Response Rate [Time Frame: Induction therapy (up to 60 days)]

   Percentage of participants who achieved a complete response (CR). A CR was defined as normalization of blood counts and a marrow showing less than 5% blasts occurring on or before day 60.

4. Disease-free Survival (DFS) [Time Frame: Duration of study (Up to 10 years)]

   Disease free survival (DFS) is defined as the time from documentation of first CR at any time to the first of relapse or death from any cause in participants who achieved a CR.

5. DFS Rate One Year After Completing the Planned Continuation Phase [Time Frame: 30 months]

Eligibility Criteria

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Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	18 Years to 59 Years (Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

1. Documentation of Disease:
   - Unequivocal diagnosis of AML (> 20% blasts in the bone marrow based on the WHO classification), excluding M3 (acute promyelocytic leukemia). Patients with neurologic symptoms suggestive of CNS leukemia are recommended to have a lumbar puncture. Patients whose CSF is positive for AML blasts are not eligible.
   - Documented FLT3 mutation (ITD or point mutation), determined by analysis in a protocol- designated FLT3 screening laboratory.
2. Age Requirement:
   - Age ≥ 18 and < 60 years
3. Prior Therapy:
   - No prior chemotherapy for leukemia or myelodysplasia with the following exceptions:
     - emergency leukapheresis
     - emergency treatment for hyperleukocytosis with hydroxyurea for ≤ 5 days
     - cranial RT for CNS leukostasis (one dose only)
     - growth factor/cytokine support
   - AML patients with a history of antecedent myelodysplasia (MDS) remain eligible for treatment on this trial, but must not have had prior cytotoxic therapy (e.g., azacitidine or decitabine)
   - Patients who have developed therapy related AML after prior RT or chemotherapy for another cancer or

disorder are not eligible.

4. Cardiac Function: Patients with symptomatic congestive heart failure are not eligible.
5. Initial Laboratory Value: Total bilirubin < 2.5 x ULN (Upper Limit of Normal)
6. Pregnancy and Nursing Status:
   - Non-pregnant and non-nursing due to the unknown teratogenic potential of midostaurin in humans, pregnant or nursing patients may not be enrolled.
   - Women of childbearing potential must have a negative serum or urine pregnancy test within a sensitivity of at least 50 mIU/mL within 16 days prior to registration.
   - Women of child-bearing potential must either commit to continued abstinence from heterosexual intercourse or commit to TWO acceptable methods of birth control:
     - one highly effective method (eg, IUD, hormonal (non-oral contraceptive), tubal ligation, or partner's vasectomy) and
     - one additional effective method (e.g., latex condom, diaphragm or cervical cap)
   - The two acceptable methods of birth control must be used AT THE SAME TIME, before beginning midostaurin/placebo therapy and continuing for 12 weeks after completion of all therapy.
   - Note that oral contraceptives are not considered a high effective method because of the possibility of a drug interaction with midostaurin.
   - Women of childbearing potential is defined as a sexually active mature woman who has not undergone a hysterectomy or who has not had menses at any time in the preceding 24 consecutive months.
   - Men must agree not to father a child and must use a latex condom during any sexual contact with women of childbearing potential while taking midostaurin/placebo and for 12 weeks after therapy is stopped, even if they have undergone a successful vasectomy.

Contacts and Locations

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Information from the National Library of Medicine NIH NLM

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT00651261***

Show 176 Study Locations

Sponsors and Collaborators

Alliance for Clinical Trials in Oncology

National Cancer Institute (NCI)

Novartis Pharmaceuticals

Investigators

Study Chair: Richard M. Stone, MD Dana-Farber Cancer Institute

More Information

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Publications of Results:

Stone RM, Dohner H, Ehninger G, et al.: CALGB 10603 (RATIFY): A randomized phase III study of induction (daunorubicin/cytarabine) and consolidation (high-dose cytarabine) chemotherapy combined with midostaurin or placebo in treatment-naive patients with FLT3 mutated AML. [Abstract] J Clin Oncol 29 (Suppl 15): A-TPS199, 2011.

Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, Thiede C, Prior TW, Döhner K, Marcucci G, Lo-Coco F, Klisovic RB, Wei A, Sierra J, Sanz MA, Brandwein JM, de Witte T, Niederwieser D, Appelbaum FR, Medeiros BC, Tallman MS, Krauter J, Schlenk RF, Ganser A, Serve H, Ehninger G, Amadori S, Larson RA, Döhner H. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. N Engl J Med. 2017 Aug 3;377(5):454-464. doi: 10.1056/NEJMoa1614359. Epub 2017 Jun 23.

Stone RM, Fischer T, Paquette R, Schiller G, Schiffer CA, Ehninger G, Cortes J, Kantarjian HM, DeAngelo DJ, Huntsman-Labed A, Dutreix C, del Corral A, Giles F. Phase IB study of the FLT3 kinase inhibitor midostaurin with chemotherapy in younger newly diagnosed adult patients with acute myeloid leukemia. Leukemia. 2012 Sep;26(9):2061-8. doi: 10.1038/leu.2012.115. Epub 2012 Apr 27.

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ClinicalTrials.gov Identifier:	NCT00651261 History of Changes
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Keywords provided by Alliance for Clinical Trials in Oncology:

- adult acute basophilic leukemia
- adult acute eosinophilic leukemia
- adult acute lymphoblastic leukemia
- adult acute megakaryoblastic leukemia (M7)
- adult acute minimally differentiated myeloid leukemia (M0)
- adult acute monoblastic leukemia (M5a)
- adult acute monocytic leukemia (M5b)
- adult acute myeloblastic leukemia with maturation (M2)
- adult acute myeloblastic leukemia without maturation (M1)
- adult acute myeloid leukemia with 11q23 (MLL) abnormalities
- adult acute myeloid leukemia with inv(16)(p13;q22)
- adult acute myeloid leukemia with t(16;16)(p13;q22)
- adult acute myeloid leukemia with t(8;21)(q22;q22)
- adult acute myelomonocytic leukemia (M4)
- adult erythroleukemia (M6a)
- adult pure erythroid leukemia (M6b)
- untreated adult acute myeloid leukemia

Additional relevant MeSH terms:

- Leukemia
- Leukemia, Myeloid
- Leukemia, Myeloid, Acute
- Neoplasms by Histologic Type
- Neoplasms
- Dexamethasone acetate
- Dexamethasone
- Midostaurin
- Cytarabine
- Daunorubicin
- Peripheral Nervous System Agents
- Physiological Effects of Drugs
- Gastrointestinal Agents
- Glucocorticoids
- Hormones
- Hormones, Hormone Substitutes, and Hormone Antagonists
- Antineoplastic Agents, Hormonal
- Antineoplastic Agents
- Protease Inhibitors

BB 1101
Staurosporine
Anti-Inflammatory Agents
Antiemetics
Autonomic Agents
Enzyme Inhibitors
Molecular Mechanisms of Pharmacological Action
Antimetabolites, Antineoplastic
Antimetabolites
Antiviral Agents
Anti-Infective Agents