Randomized Phase III Study of Decitabine +/- Hydroxyurea (HY) Versus HY in Advanced Proliferative CMML (GFM-DAC-CMML)

ClinicalTrials.gov Identifier: NCT02214407

Recruitment Status : Recruiting
First Posted : August 12, 2014
Last Update Posted : July 12, 2017

See **Contacts and Locations**

Sponsor:
Groupe Francophone des Myelodysplasies

Collaborator:
Janssen-Cilag Ltd.

Information provided by (Responsible Party):
Groupe Francophone des Myelodysplasies

Study Description

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Brief Summary:

This is a phase III, two-arm, randomized, stratified, multicenter, open-label study with individual therapeutic benefit aim:

Decitabine (DAC) with or without Hydroxyurea (HY) versus HY in patients with advanced proliferative Chronic Myelomonocytic Leukemia (CMML)

The primary objective of the study is to compare between the two arms Event-free Survival (EFS).

Secondary objectives are to compare between both arms:

Overall Survival (OS) Cumulative incidence of AML Overall and Complete Response Rates at 3 and 6 cycles according to IWG 2006 criteria modified for CMML Response duration Toxicity (hematological and non hematological) Prognostic factors

Condition or disease	Intervention/treatment	Phase
MDS	Drug: Decitabine Drug: HYDROXYUREA	Phase 3

Detailed Description:

ARM A: DECITABINE (DAC)

Decitabine (DAC) will be administered at 20 mg/m2 intravenously daily for 5 days every 28 days.

Treatment will be delayed at the discretion of the investigator (up to D56) for febrile neutropenia (≥ 38.5°C; absolute neutrophil count [ANC], < 1,000/µL), clinical and/or microbiologic infection with grade 3 to 4 neutropenia (ANC < 1,000/µL), or hemorrhage with grade 4 thrombocytopenia (< 25,000 platelets/µL). If renal or hepatic dysfunction occurs, treatment will be stopped until resolution or withheld if dysfunction persists more than 4 days. Persistent grade 4 thrombocytopenia or neutropenia beyond D49 will mandate bone marrow evaluation.

Treatment will be continued until an event is reached. Events and thus study exit will be acknowledged only after agreement between the investigator and a Trial Committee.

Allopurinol, 300mg/d, will be started at the time of inclusion; hydration during treatment will be administered to all patients. In (the rare) case of necessity, prophylactic anti-emetics could be given.

Hydroxyurea may be added during the first 3 cycles if WBC counts > 30 G/L, and mandatory if WBC > 50 G/L. The daily dose will be adapted to maintain WBC below 15 to 20 G/L.

ARM B: HYDROXYUREA (HY)

Hydroxyurea (HY) 1g/d once daily, with dose adjustments (up to 4g/d) to maintain a WBC count between 5 and 10 G/L. Allopurinol, 300mg/d started at the time of inclusion will be administered to all patients.

Treatment will be continued until an event is reached. Events and thus study exit will be acknowledged only after agreement between the investigator and a Trial Committee. This is intended to prevent early dropout, notably in the HY arm.

Dose escalation will be performed by steps of 0.5 g/d, up to 4 g/d, if the WBC has been reduced by less than 20% and remains > 15 G/L. HY will then be adapted to maintain a WBC count between 5 and 10 G/L. HY will be lowered if platelets decrease by > 30 X 109/L (if initially below 100 X 109L). HY will be discontinued in cases of grade 4 thrombocytopenia or neutropenia, and reintroduced at a lower dose after recovery to grade ≤ 3. Persistent grade 4 thrombocytopenia or neutropenia after a 4 week discontinuation will mandate bone marrow evaluation.

Study Design

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Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	168 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	A Randomized Phase III Study of Decitabine (DAC) With or Without Hydroxyurea (HY) Versus HY in Patients With Advanced Proliferative Chronic Myelomonocytic Leukemia (CMML)
Actual Study Start Date :	October 31, 2014
Estimated Primary Completion Date :	December 2017
Estimated Study Completion Date :	October 2018

Drug Information available for: Hydroxyurea
Decitabine

Genetic and Rare Diseases Information Center resources: Chronic Myelomonocytic Leukemia

U.S. FDA Resources

Arms and Interventions

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Arm	Intervention/treatment
Experimental: ARM A: DECITABINE (DACOGEN) Decitabine (DAC) will be administered at 20 mg/m2 intravenously daily for 5 days every 28 days. Allopurinol, 300mg/d, will be started at the time of inclusion; hydration during treatment will be administered to all patients. In (the rare) case of necessity, prophylactic anti-emetics could be given. Hydroxyurea may be added during the first 3 cycles if WBC counts > 30 G/L, and mandatory if WBC > 50 G/L. The daily dose will be adapted to maintain WBC below 15 to 20 G/L.	Drug: Decitabine Decitabine (DAC) will be administered at 20 mg/m2 intravenously daily for 5 days every 28 days. Hydroxyurea may be added during the first 3 cycles if WBC counts > 30 G/L, and mandatory if WBC > 50 G/L. The daily dose will be adapted to maintain WBC below 15 to 20 G/L. Treatment will be continued until an event is reached. Events and thus study exit will be acknowledged only after agreement between the investigator and a Trial Committee. Other Name: DACOGEN
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Outcome Measures

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Primary Outcome Measures :

1. compare between the two arms Event-free Survival (EFS) [Time Frame: 3 months]

   Comparison of Event-free Survival between both arms. Events will include

   - Death from any cause
   - Disease Progression, defined as one of the following: (i) at any time point: transformation to AML according to WHO criteria ; (ii) after at least 6 cycles of treatment: doubling of bone marrow blasts to > 10%, and worsening of cytopenias lasting for > 4 weeks ; (iii) after at least 3 cycles of treatment: Progression of myeloproliferation (despite maximal HY or DAC dosing; in the absence of concomitant infection) defined as: ≥ 50% increase in spleen size as determined by an imaging technique or doubling in WBC or occurrence of a previously undiagnosed extramedullary localization of the disease.

Secondary Outcome Measures :

1. Overall Survival (OS) [Time Frame: 7 month]

   Overall survival compared between both Arm of treatment (decitabine and hydroxyurea)

2. Cumulative incidence of AML [Time Frame: 7 month]

   Comparaison of Cumulative incidence of AML between both arm of treatment (decitabine and hydroxyurea)

3. Overall and Complete Response Rates [Time Frame: 3 month]

   Overall and Complete Response Rates at 3 and 6 cycles according to IWG 2006 criteria modified for CMML

4. Response duration [Time Frame: 3 month]

   Comparison of response duration after 3 month and 6 month of treatment between both arm of treatment (decitabine and hydroxyurea)

5. Toxicity [Time Frame: 1 month]

   hematological and non hematological

6. Prognostic factors [Time Frame: 3 month]

   Prognostic factors of Event Free Survival with decitabine and hydroxyurea

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 and older (Adult, Senior)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Age ≥ 18
- CMML diagnosis according to WHO criteria Stable excess in blood monocytes, > 1 G/L Lack of bcr-abl rearrangement (or Philadelphia chromosome) Bone marrow blast cells <

20% Dysplasia of at least one lineage or clonality marker or blood monocytosis during more than 3 months w/o other explanation Blood and marrow smears will be reviewed at each country's level, but morphologist meetings at the 3 country level are planned for better harmonization and review of difficult cases

- WBC ≥ 13 G/L Measured on two successive CBC at least two weeks apart, outside of a context of infection.
- Either D1 or D2

D1: At least two of the following criteria, reviewed at each country's level: (modified from Wattel et al. Blood 1996) Marrow blasts >= 5 % Clonal cytogenetic abnormality (other than t (5;12) (q33; p13) and isolated loss of Y chromosome) Anemia (Hb < 10 g/dL) ANC > 16 G/l (in absence of infection) Thrombocytopenia (platelet count < 100 G/L) Splenomegaly > 5 cm below costal margin (spleen size should also be measured by an imaging technique)

Or:

D2: Extramedullary involvement: Including documented cutaneous, pleural or pericardial effusion.

- No prior treatment (except supportive care, or ESA, or short term (< 6 weeks) HY in patients presenting with high WBC counts)
- Performance status 0-2 on the Eastern Cooperative Oncology Group (ECOG) Scale.
- Adequate organ function including the following Hepatic : total bilirubin < 1.5 times upper limit of normal (ULN) (except moderate unconjugated hyperbilirubinemia due to intra medullary hemolysis or Gilbert syndrome) , alanine transaminase (ALT) and aspartate transaminase (AST) < 3xULN Renal : serum creatinine < 2 x ULN
- Signed Informed consent
- Negative pregnancy and adequate contraception (including in male patients wishing to father) if relevant.

Exclusion Criteria:

- Myeloproliferative / myelodysplastic syndrome other than CMML
- CMML with t(5 ;12) or PDGFBR rearrangement that may receive imatinib
- Patients eligible for allogeneic bone marrow transplantation with an identified donor
- Pregnant or breastfeeding
- Performance status > 2 on the ECOG Scale.
- Serious concomitant systemic disorder, including active bacterial, fungal or viral infection that in the opinion of the investigator would compromise the safety of the patient and/or his/her ability to complete the study
- Prior malignancy (except in situ cervix carcinoma, limited basal cell carcinoma, or other tumors if not active during the last 3 years)

Contacts and Locations

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Information from the National Library of Medicine

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): ***NCT02214407***

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More Information

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Responsible Party: Groupe Francophone des Myelodysplasies

ClinicalTrials.gov Identifier:	NCT02214407 History of Changes
Other Study ID Numbers:	**GFM-DAC-CMML**
First Posted:	August 12, 2014 Key Record Dates
Last Update Posted:	July 12, 2017
Last Verified:	July 2017

Additional relevant MeSH terms:

Benzocaine	Antimetabolites
Decitabine	Molecular Mechanisms of Pharmacological
Azacitidine	Action
Allopurinol	Antineoplastic Agents
Hydroxyurea	Enzyme Inhibitors
Anesthetics, Local	Gout Suppressants
Anesthetics	Antirheumatic Agents
Central Nervous System Depressants	Free Radical Scavengers
Physiological Effects of Drugs	Antioxidants
Sensory System Agents	Protective Agents
Peripheral Nervous System Agents	Antisickling Agents
Antimetabolites, Antineoplastic	Nucleic Acid Synthesis Inhibitors