10-day decitabine versus conventional chemotherapy (*3+7*) followed by allografting in AML patients >= 60 years: a randomized phase III study of the EORTC Leukemia Group, CELG, GIMEMA and German MDS Study Group

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The primary objective of this study is to compare, in a randomized phase III trial, the effect of 10-day decitabine at a dose of 20 mg/m2 versus conventional induction chemotherapy (*3+7*) on OS in older AML patients.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON44877

Source
ToetsingOnline

Brief title
EORTC-1301-LG - AML21: InDACtion vs. Induction

Condition

- Leukaemias

Synonym
Acute myeloid leukemia, AML

Research involving

Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: Janssen Pharmaceutica,KWF subsidie t.b.v. datamanagement wordt aangevraagd

Intervention

Keyword: AML, Dacogen, Decitabine, Leukemia

Outcome measures

Primary outcome

Overall survival

Secondary outcome

CR/CRi rate, response rate (CR/CRi and PR), overall CR/CRi rate, DFS, PFS;

Safety and toxicity;

Transplantation feasibility: percentage of patients transplanted;

Outcome post-transplantation: PFS, incidence of relapse or progression, and

incidence of NRPM (or TRM);

Days of staying in hospital and transfusion needs;

HRQoL (EORTC QLQ-C30, ELD14);

The prognostic value of baseline physical and functional conditions using a

comprehensive geriatric assessment tools (short physical performance battery

[SPPB] and activities of daily living [ADL]) on treatment outcome.

Study description

Background summary

1. The OS of older AML patients has not been improved during the last decades with intensive chemotherapy based on cytarabine combined with an anthracycline (*3+7*);

2. Next generation sequencing technology reveals that mutations in genes involved in epigenetics are frequently mutated in AML (e.g. DNMT3a), suggesting an important role of epigenetics in the pathophysiology of AML;

3. Prospective randomized trials, though small, have shown that intensive chemotherapy or low-dose Ara-C is superior to best supportive care. Interestingly, only decitabine (given in a 5-day schedule), but not intensive chemotherapy (Ref. 17), has been shown to be superior to low-dose Ara-C;

4. A retrospective analysis revealed that epigenetic therapy (either azacitidine or decitabine) is associated with similar survival rates as intensive chemotherapy in older patients (n=671) with newly diagnosed AML (Ref. 40). Although in the final analysis azacitidine and decitabine were combined, decitabine was associated with improved median OS compared with azacitidine;

5. The recently published encouraging phase 2 data with the 10-day decitabine schedule suggest that decitabine results in similar CR rates compared with intensive chemotherapy. It should be noted that many studies illustrate that hypomethylating agents impact on survival without inducing CR, suggesting that similar CR rates between 10-day decitabine and conventional chemotherapy might translate in survival benefit for the 10-day decitabine schedule;

6. AlloHCT also offers the opportunity for cure among older AML patients, therefore treatment strategies should aim to allograft older AML patients;

7. Decitabine treatment can lead to very interesting cure rates when used as "bridging" to allografting.

Based on the data summarized above, we think the time has come to compare conventional intensive chemotherapy based on cytarabine combined with an anthracycline (*3+7*) in a prospective randomized trial with the hypomethylating agent decitabine to determine the optimal backbone for the

treatment of older AML patients. We hypothesize that decitabine at a daily dose of 20 mg/m² starting with the 10-day schedule followed by an alloHCT or by continuation of 5-days decitabine cycles is superior to conventional intensive chemotherapy in older AML patients.

Study objective

The primary objective of this study is to compare, in a randomized phase III trial, the effect of 10-day decitabine at a dose of 20 mg/m2 versus conventional induction chemotherapy (*3+7*) on OS in older AML patients.

Study design

This is an open-label, randomized, multicenter phase III study to compare two different treatment strategies in older patients with AML: conventional *3+7* chemotherapy (control arm) and hypomethylating drug decitabine (experimental arm).

Patients will be centrally randomized. A minimization technique will be used for random treatment allocation. Stratification factors will be:
type of AML (de novo vs secondary AML), age at randomization (60-64 vs 65-69 vs >70 yrs) and institution.

Intervention

Treatment with conventional *3+7* chemotherapy (control arm) versus treatment with hypomethylating drug decitabine (experimental arm).

Study burden and risks

Patients treated in the studyarm may have less or shorter hospitalisations during the first cycles.

Extra collection of bone marrow at diagnosis (during a regular bone marrow punction); At ca. 10 times extra collection of blood (mostly during a regular venapunction); Extra collection of saliva at diagnosis. For specfications see E6.

Fill out questionnaires about quality of life and geriatric assessment up to 5 times.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Age >= 60 years; WHO Performance status: <= 2;* Eligible for standard intensive chemotherapy;*Patients of reproductive potential should use adequate birth control measures, as defined by the investigator, during the study treatment period and for at least 3 months after the last study treatment. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly;* Have newly diagnosed AML that is cytopathologically confirmed according to WHO classification (Patients can be diagnosed with AML preferably two months prior to randomization);*De novo or secondary AML is allowed;*WBC is <=30x109/L (measured at most 72 hours prior to randomization);* The following laboratory assessments should be done prior to randomization and should be within the following range:;* SGOT (AST) and SGPT (ALT) < 2.5 x the upper limit of normal range (at the laboratory where the analyses were performed) unless considered AML-related;* Total serum bilirubin level < 2.5 x the upper limit of normal range (at the laboratory where the analyses were performed) unless considered AML-related or due to Gilbert*s syndrome;* Serum creatinine concentration < 2.5 x the upper limit of normal range (at the laboratory where the analyses were performed) unless considered AML-related;* The following treatments for previous MDS or MPN are allowed as

long as treatment has stopped one month before inclusion:;-Growth factors, thrombomimetics, immunosuppression (cyclosporin A, steroids, Antithymocyte globulin etc.), chelation, interferons, anagrelide;-Lenalidomide, low-dose chemotherapy (low-dose melphalan, hydroxyurea, low-dose cytarabine etc.), tyrosine-kinase inhibitors, histone deacetylase inhibitors (e.g. Valproic acid, panobinostat etc.), mTOR inhibitors, other experimental treatment that is not based on inhibition of DNA methyltransferase;* Before patient registration/randomization, written informed consent must be given according to ICH/GCP and national/local regulations

Exclusion criteria

* Presence of acute promyelocytic leukaemia (APL, i.e. AML-M3 with t(15;17)(q22;q12); PML-RARA fusion gene and cytogenetic variants);* Presence of blast crisis of chronic myeloid leukaemia;* Presence of active central nervous system (CNS) leukaemia. Local prophylaxis for the CNS compartment as per local standard practice is permitted. ;* Prior treatment for AML (relapsed AML is not allowed), these are any antileukaemic therapy including other systemic anticancer or investigational agents and hypomethylating agents (decitabine, 5-azacytidine). Exception: Treatment with Hydroxyurea (HU) is allowed to control the leukocytosis if given preferably for less than 5 days.;* Prior treatment for MDS or MPN with:;-hypomethylating agents (decitabine, 5-azacytidine), OR;-intensive chemotherapy or transplantation within the last three years;* Presence of concomitant severe cardiovascular disease which would make intensive chemotherapy impossible, i.e. uncontrolled arrhythmias requiring chronic treatment, congestive heart failure or symptomatic ischemic heart disease, reduced left ventricular function assessed by MUGA scan or echocardiogram.;* Presence of any malignancy (except basal and squamous cell carcinoma of the skin) for which the patient received systemic anticancer treatment within 6 months prior to randomization.;* Presence of active uncontrolled infection;* Presence of any psychological, familial, sociological or geographical condition in the opinion of the investigator potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-12-2014
Enrollment:	150
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cytarabine
Generic name:	Cytarabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Dacogen
Generic name:	Decitabine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Daunorubicin
Generic name:	Daunorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Etoposide
Generic name:	Etoposide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Idarubicin
Generic name:	Idarubicin
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	20-10-2014
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	19-11-2014
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	20-02-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	29-06-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	06-12-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	23-12-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO
Date: 24-02-2017

Application type: Amendment

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Approved WMO
Date: 09-06-2017

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 04-08-2017

Application type: Amendment

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Approved WMO
Date: 11-04-2023

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 15-02-2024

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 11-03-2024

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-001486-27-NL
ClinicalTrials.gov	NCT02172872
CCMO	NL49937.098.14