

# Samenvatting H102

## Titel

HOVON 102 AML / SAKK 30/09, Randomized study with a run-in feasibility phase to assess the added value of Clofarabine in combination with standard remission-induction chemotherapy in patients aged 18-65 years with previously untreated acute myeloid leukemia (AML) or myelodysplasia (MDS) (RAEB with IPSS  $\geq 1.5$ )”

**Onderzoek naar de verdraagbaarheid en de werkzaamheid van Clofarabine, wanneer het wordt toegevoegd aan de standaard inductie chemotherapie bij patiënten, tussen 18 en 65 jaar, met onbehandelde acute myeloïde leukemie (AML) of myelodysplasie type refractaire anemie met toename blasten (RAEB)**

## Achtergrond

Acute Myeloid Leukemia (AML) is a bone marrow malignancy of progenitor cells of the myeloid cell lineage (1). AML is classified according to the World Health Organization (WHO) classification together with myelodysplastic syndromes (MDS) which resemble AML (2,5). The myelodysplastic syndromes are a heterogeneous group of hematopoietic disorders among which the refractory anemia with excess of blasts (RAEB) with high ( $\geq 1.5$ ) IPSS is one of the most prognostically unfavourable subtypes frequently evolving to AML (3, 4,5).

Het onderzoek betreft de eerste fase van de behandeling, de inductiebehandeling. Bij het onderzoek gaat het om de vraag of toevoeging van een nieuw geneesmiddel, het middel clofarabine, aan de eerste twee inductiekuren het behandelingsresultaat kan verbeteren. Omdat het een nieuw middel betreft moet tevens de verdraagbaarheid van de toevoeging van clofarabine aan de kuren worden vastgesteld. Er zijn gegevens uit eerder onderzoek dat clofarabine werkzaam is tegen leukemie bij oudere patiënten en bij patiënten die al eerder zijn behandeld voor leukemie en bij wie de leukemie de kop weer had opgestoken. De vraag is nu of toevoeging van clofarabine bij nieuwe patiënten aan de huidige behandeling de uitkomst kan verbeteren. Om die reden wordt deze onderzoeksvraag gesteld in dit onderzoek.

Indien u besluit aan dit onderzoek mee te doen, zal door loting worden bepaald of uw behandeling zal bestaan uit de standaard chemotherapie *zonder* het middel clofarabine of de standaard behandeling *met* het middel clofarabine. De kans op loting voor behandeling met of zonder het middel clofarabine is even groot. De loting (ook wel randomisatie genoemd) is nodig om op onafhankelijke wijze de twee behandelingen met elkaar te kunnen vergelijken. Uw behandelend arts en de onderzoekers hebben géén invloed op de uitslag van de loting.

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Aan het begin van dit onderzoek wordt uit 3 mogelijke doseringen de verdraagbaarheid van clofarabine in combinatie met de andere celdodende middelen bepaald en wordt het dosisniveau van clofarabine voor de rest van de studie gekozen. Dit wordt deel A genoemd van de studie. Na keuze van de uiteindelijke dosering gaat de studie in deel B verder met één dosis van clofarabine.

Deze informatie gaat over deel A van de studie.

## Doel

### Studieopzet

**Part A:** A prospective feasibility study of remission induction chemotherapy combined with Clofarabine at a maximum of 3 dose levels (10, 15, 20 mg/m<sup>2</sup>).

**Part B:** Subsequent to completion of the feasibility study (part A), the value of Clofarabine at the

selected dose level when combined with standard induction chemotherapy will be investigated in a

phase III randomized study.

The choice of the chemotherapeutic regimens of remission induction

### Treatment design

#### 7.2.1 Remission induction treatment

The study is designed as a randomized study in which patients will be randomized to receive idarubicin-cytarabine alone or idarubicin-cytarabine combined with intravenously administered

Clofarabine (respective study arms A and B - cycle I) and amsacrine-cytarabine alone or amsacrine-cytarabine

plus Clofarabine (cycle II). Patients with newly diagnosed AML (except acute promyelocytic leukemia), or RAEB with IPSS  $\geq 1.5$  (see appendices A and B), meeting all eligibility

criteria will be included.

#### 7.2.2 Post remission treatment according to risk assessment

All patients will receive 2 cycles for induction and then according their prognostic risk assessment

(see section 5.4.2 and 5.8) proceed to postremission therapy (chemotherapy cycle III, autoSCT or alloSCT).

Patients in CR, unless they proceed to alloSCT, will undergo stem cell mobilization with G-CSF and

stem cell collection after the second induction cycle. Patients with an adequate harvest who fulfill the

eligibility criteria will proceed to busulfan-cyclophosphamide ablation + autoPBSCT.

All other patients (considered not eligible for an alloSCT or autoPBSCT) will be offered the chemotherapy cycle III: mitoxantrone and etoposide.

- *Good risk* (GR) patients will receive a third cycle of chemotherapy (cycle III: mitoxantrone plus

etoposide). In case the TRM risk following alloSCT is estimated to be very low ( $\leq 10-15\%$ ), alloSCT

can be considered. This applies to patients with an optimal donor, with an EBMT risk score of 0 or 1

and a comorbidity score of 0.

- *Intermediate risk* (IR) patients with a HLA matched related or 10/10 molecular matched

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unrelated donor will proceed to alloSCT if the risk of transplant related mortality of such a transplant is assessed to be less than 20%. This applies to patients with a sibling or a 10/10 matched unrelated donor with an EBMT risk score  $\leq 3$  and a HCT-CI  $\leq 2$ . If such a transplant is not elected, the autologous transplantation is the second choice. If this is not possible, as the third choice patients will receive a third cycle of chemotherapy (cycle III: mitoxantrone plus etoposide).

- *Poor risk* (PR) patients with a HLA matched related or unrelated donor may proceed to alloSCT as soon as they have entered CR provided the risk for TRM risk  $< 40\%$ . This applies to patients with an EBMT risk score  $\leq 5$ . If patients are identified as poor risk following cycle I and logistically there are no impediments, the patient may proceed to alloSCT as soon as possible after cycle I. If an alloSCT is not possible or elected, an autologous transplant is the second option and a third cycle of chemotherapy is the third option

- *Very poor risk* (VPR) patients with a HLA matched related or unrelated donor may proceed to alloSCT as soon as they have entered CR. This applies to patients with an EBMT risk score  $\leq 5$  and irrespective of HCT-CI. Also, a 9/10 unrelated donor, a haploidentical family donor (preferably the mother) or a cord blood with sufficient matching and cell numbers can be considered in experienced centres. If patients are already distinguished as very poor risk following cycle I and logistically it would be possible to immediately proceed to alloSCT at that point, the alloSCT might be planned as soon as possible after cycle I. If an alloSCT is not possible, an autologous transplant is a second and a third cycle of chemotherapy is a third possible option

For further information on risk group definition see appendices E and F.

### Populatie

Patients with previously untreated AML (except acute promyelocytic leukemia) or MDS RAEB with IPSS  $\geq 1.5$ , age 18-65 years.

### Interventie/geneesmiddel

Clofarabine

### Eindpunten

#### Primary objectives

For part A of the study:

ϕ To determine the feasibility of Clofarabine when given at three possible dose levels together

with standard induction cycles I and II in patients with AML/ RAEB with IPSS  $\geq 1.5$  in a prospective comparison to standard induction cycles I and II without Clofarabine.

For part B of the study:

ϕ To evaluate the effect of Clofarabine at the selected feasible dose level when combined with

remission induction chemotherapy cycles I and II as regards clinical outcome ("event-free

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survival”) in comparison to remission induction cycles I and II with no addition of Clofarabine in a phase III study.

### Secondary objectives

For part A of the study:

φ To investigate the clinical efficacy of Clofarabine in combination with remission induction chemotherapy cycles I and II with regard to complete remission rate at different dose levels of Clofarabine.

For part B of the study:

φ To investigate the clinical efficacy of Clofarabine with regard to the complete remission rate,

disease free survival (DFS), risk of relapse and overall survival (OS) when combined with remission induction chemotherapy cycles I and II in all patients.

φ To investigate the clinical efficacy of Clofarabine when combined with remission induction chemotherapy cycles I and II in molecularly and cytogenetically distinguishable subsets with regard to the complete remission rate, disease free survival (DFS), risk of relapse and overall survival (OS).

φ To investigate the tolerance and toxicity of Clofarabine in combination with remission induction chemotherapy cycles I and II.

φ To assess the effect of Clofarabine on peripheral CD34 cell numbers for autologous peripheral blood transplantation.

φ To determine the prognostic value of molecular markers and gene expression profiles of the leukemia assessed at diagnosis.

φ To evaluate the treatment effects according minimal residual disease (MRD) measurements

following therapy by standardized sampling of marrow/blood.

φ To evaluate the outcome of allogeneic sibling or unrelated donor SCT and autologous SCT in

cytogenetically and molecularly defined prognostic subgroups of patients.

### Inclusiecriteria

Age 18-65 years, inclusive

φ Subjects with

- a cytopathologically confirmed diagnosis of AML according WHO classification (excluding acute promyelocytic leukaemia) **or**

- a diagnosis of refractory anemia with excess of blasts (RAEB) and IPSS score  $\geq 1.5$  **or**

- patients with therapy-related AML/RAEB **or**

- patients with biphenotypic leukemia (Appendices A1 and A2).

φ Adequate renal and hepatic function tests as indicated by the following laboratory values:

- Serum creatinine  $\leq 1.0$  mg/dl ( $\leq 88.7$  micromol/L); if serum creatinine  $> 1.0$  mg/dl ( $> 88.7$

micromol/L), then the glomerular filtration rate (GFR) must be  $> 60$  ml/min/1.73 m<sup>2</sup> as

calculated by the Modification of Diet in Renal Disease equation where the predicted

GFR (ml/min/1.73 m<sup>2</sup>) =  $186 \times (\text{Serum Creatinine in mg/dl})^{-1.154} \times (\text{age in years})^{-0.023} \times$

(0.742 if patient is female)  $\times$  (1.212 if patient is black)

*NOTE: if serum creatinine is measured in micromol/L, recalculate it in mg/dl according to the equation: 1 mg/dl = 88.7 micromol/L and used above mentioned formula.*

- Serum bilirubin  $\leq 1.5 \times$  upper limit of normal (ULN)

- Aspartate transaminase (AST)/alanine transaminase (ALT)  $\leq 2.5 \times$  ULN

- Alkaline phosphatase  $\leq 2.5 \times$  ULN

φ WHO performance status 0, 1 or 2 (see Appendix I)

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φ Written informed consent

### Exclusiecriteria

- Acute promyelocyten leukemie
- Eerdere behandeling voor AML of RAEB met uitzondering van hydroxyurea
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φ Previous treatment for AML or RAEB, except φ Concurrent history active malignancy in two past years prior to diagnosis except for:

- basal and squamous cell carcinoma of the skin
- in situ carcinoma of the cervix

Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, pulmonary disease etcetera),

φ Cardiac dysfunction as defined by:

- Myocardial infarction within the last 6 months of study entry, or
- Reduced left ventricular function with an ejection fraction < 50% as measured by MUGA scan or echocardiogram (another method for measuring cardiac function is acceptable), or
- Unstable angina, or
- Unstable cardiac arrhythmias

φ Pregnant or lactating females

φ Unwilling or not capable to use effective means of birth control

### Aandachtspunten

- **Medicatie inhibitoren/ induceerders**

- **Bijwerkingen**

#### Bijwerkingen van clofarabine

Clofarabine kan de bekende bijwerkingen van cytostatica zoals misselijkheid, braken en haaruitval tot gevolg hebben. Verder onderdrukt het net als de andere chemotherapie tijdelijk de bloedaanmaak. De bijwerkingen van clofarabine die verder zijn gezien in voorgaand onderzoek, zijn diarree, hoofdpijn, pijnlijke mond. Ook zijn longafwijkingen en afwijkingen aan de lever en de nier beschreven. De toediening van het geneesmiddel kan soms worden gevolgd door een huiduitslag en hartkloppingen en een snel hartritme, een koortsreactie en eventueel een verlaagde bloeddruk.

**Idarubicine** kan de de pompfunctie van het hart nadelig beïnvloeden. Hierdoor kunnen klachten optreden van kortademigheid of kunt u extra vocht vasthouden.

**Cytarabine (afkorting: Ara-C)** kan leverfunctiestoornissen, huidafwijkingen (roodheid, branderigheid) geven en klachten van diarree, buikkrimp, koorts of branderige pijnlijke ogen. In een enkel geval kunnen longafwijkingen optreden of klachten van sufheid, onzeker lopen, bewegen of moeilijk praten.

**Amsacrine** heeft als bijwerkingen misselijkheid, haaruitval en onderdrukken van de bloedaanmaak.

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