Protocol of clinical trial

Title
AML-AZA: A randomized, multicenter phase II trial to assess the efficacy of 5-azacytidine added to standard primary therapy in elderly patients with newly diagnosed Acute Myeloid Leukemia (AML)

Inclusion Criteria:

- Patients with newly diagnosed AML (except APL) according to the FAB or WHO classification, including AML evolving from MDS or other hematological diseases and AML after previous cytotoxic therapy or radiation (secondary AML).
- Bone marrow aspirate or biopsy must contain $\geq 20\%$ blasts of all nucleated cells or differential blood count must contain $\geq 20\%$ blasts. In AML FAB M6 $\geq 30\%$ of non-erythroid cells in the bone marrow must be leukemic blasts. In AML defined by cytogenetic aberrations the proportion of blasts may be $< 20\%$.
- Age $\geq 61$ years
- Informed consent, personally signed and dated to participate in the study
- Male patients enrolled in this trial must use adequate barrier birth control measures during the course of the 5-azacytidine treatment and for at least 3 months after the last administration of 5-azacytidine

Exclusion Criteria:

- Patients who are not eligible for standard chemotherapy as described in chapter 5.2 and 5.3
- Hyperleukocytosis (leukocytes $> 20,000/\mu l$) at study entry. These patients should be treated with hydroxyurea or receive leucocytapheresis treatment (if leukocytes $> 100,000/\mu l$) according to routine practice and entered into the study when leukocyte counts below 20,000/\mu l are reached. This applies only for the controlled part of the study.
- Patients with initial hyperleukocytosis above 20,000/\mu l can only be enrolled into the controlled part of the study, but not in the run-in dose finding part.
- Known central nervous system manifestation of AML
- Cardiac Disease: Heart failure NYHA class 3 or 4; unstable coronary artery disease (MI more than 6 months prior to study entry is permitted); serious cardiac ventricular arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted)
- Chronically impaired renal function (creatinin clearance $< 30\ \text{ml/\text{min}}$)
- Inadequate liver function (ALT and AST $\geq 2.5 \times \text{ULN}$) if not caused by leukemic infiltration
- Total bilirubin $\geq 1.5 \times \text{ULN}$ if not caused by leukemic infiltration
- Known HIV and/or hepatitis C infection
- Evidence or history of severe non-leukemia associated bleeding diathesis or coagulopathy
- Evidence or recent history of CNS disease, including primary or metastatic brain tumors, seizure disorders
- Uncontrolled active infection
- Concurrent malignancies other than AML with an estimated life expectancy of less than two years
- History of organ allograft
- Hypersensitivity to cytarabine (not including drug fever or exanthema), daunorubicin, azacytidine or mannitol
- Previous treatment of AML except hydroxyurea and up to 2 days of $\leq 100\ \text{mg/m2/d}$ cytarabine

Orphanet Database. Clinical trial 2009.
http://www.orpha.net/data/eth/DE/ID68313Eng.pdf
- Previous therapy with 5-azacytidine (i.e. for an antecedent myelodysplastic syndrome)
- Patients with investigational drug therapy outside of this trial during or within 4 weeks of study entry should be discussed with the study office whether study participation is possible
- Any severe concomitant condition, which makes it undesirable for the patient to participate in the study or which could jeopardize compliance with the protocol

### Intervention

<table>
<thead>
<tr>
<th>5-azacytidine: Experimental</th>
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<tbody>
<tr>
<td>Patients enrolled in this arm will receive standard induction and consolidation chemotherapy preceded by 5-azacytidine. These patients will additionally receive maintenance therapy with 5-azacytidine for one year after start of induction therapy.</td>
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<table>
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<th>Drug: azacitidine</th>
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<tr>
<td>Starting dose to be determined during run-in dose finding part of the study. Starting dose of the interventional drug will be most likely either 75 or 37,5mg/m²/d resp. 18mg/m²/d.</td>
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<th>Application form:</th>
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<tr>
<td>During induction therapy phase: i.v. on days -5--1 before standard chemotherapy for 1 or 2 cycles, During consolidation therapy: s.c. on days -5--1 before standard chemotherapy (2 cycles).</td>
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| During maintenance therapy: s.c. on days 1-5 on a 28day cycle till maximum one year after start of first induction therapy. |

<table>
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<th>Standard chemotherapy: Active Comparator</th>
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<th>Drug: standard chemotherapy (7+3 scheme): Daunorubicin, Cytarabine</th>
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<tr>
<td>Induction therapy: Daunorubicin 45mg/m²/d i.v.on days 3,4,5 AraC 100mg/m²/d i.v. on days 1-7</td>
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<td>Consolidation therapy: AraC 1g/m² twice a day on day 1,3,5</td>
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### Number of expected inclusions

216 patients

### Study start

July 2009

### Estimated Study Completion

December 2012

### Study phase

Phase II

### Study Design

Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study

Orphanet Database. Clinical trial 2009.  