Phase III Trial in Acute Promyelocytic Leukemia Patients (APL0406)

Purpose

Open label, randomised, phase III multicenter trial.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
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</thead>
</table>
| Leukemia  | Drug: arsenic trioxide  
Drug: idarubicin  
Drug: mercaptopurine  
Drug: methotrexate  
Drug: all-trans retinoic acid  
Drug: all-trans retinoic acid (ATRA) | Phase 3 |

Study Type: Interventional

Study Design: Allocation: Randomized  
Endpoint Classification: Efficacy Study  
Intervention Model: Parallel Assignment  
Masking: Open Label  
Primary Purpose: Treatment

Official Title: A Randomised Phase III Study to Compare Arsenic Trioxide (ATO) Combined to ATRA Versus Standard ATRA and Anthracycline-Based Chemotherapy (AIDA Regimen) for Newly Diagnosed, Non High-Risk Acute Promyelocytic Leukemia

Resource links provided by NLM:

Genetics Home Reference related topics: acute promyelocytic leukemia  
familial acute myeloid leukemia with mutated CEBPA

MedlinePlus related topics: Acute Myeloid Leukemia  
Arsenic  
Leukemia

Drug Information available for: Mercaptopurine  
Methotrexate  
Tretinoin  
Arsenic trioxide  
Arsenic  
Methotrexate sodium  
Idarubicin hydrochloride

U.S. FDA Resources

Further study details as provided by Gruppo Italiano Malattie EMatologiche dell’Adulto:

Primary Outcome Measures:

- Event-free survival [Time Frame: At maximum 3.5 years from study entry] [Designated as safety issue: No]
  
As of 14th September 2010, all patients needed to evaluate the primary endpoint have been recruited.

Secondary Outcome Measures:

- Rate of hematological complete remission [Time Frame: At maximum 60 days from induction therapy start] [Designated as safety issue: No]
- Overall survival rate [Time Frame: At 2 years from study entry] [Designated as safety issue: No]
- Rate of cumulative incidence of relapse [Time Frame: At 2 years from study entry] [Designated as safety issue: No]
- Incidence of hematological and non-hematological toxicity episodes during treatment as assessed by CTC-NCI [Time Frame: At maximum 60 days from induction therapy start and at maximum 225 days from consolidation therapy start] [Designated as safety issue: Yes]
- Rate of molecular remission after 3rd consolidation course [Time Frame: At maximum 225 days from consolidation therapy start] [Designated as safety issue: No]
- Assessment of acute promyelocytic leukemia/RARα transcript level reduction after induction and during consolidation therapy [Time Frame: At maximum 60 days from induction therapy start and at maximum 225 days from consolidation therapy start] [Designated as safety issue: No]
- Quality of life at the end of induction therapy and at the end of the 3rd consolidation course [Time Frame: At maximum 60 days from induction therapy start and at maximum 225 days from consolidation therapy start] [Designated as safety issue: No]
- Event free survival [Time Frame: At 2 years from study entry] [Designated as safety issue: No]
- Total hospitalization days during study therapy [Time Frame: At maximum 3.5 years from study entry] [Designated as safety issue: No]
- Event-free survival rate in the two arms [Time Frame: At 2 years from study entry] [Designated as safety issue: No]

Enrollment: 276  
Study Start Date: August 2007  
Estimated Study Completion Date: October 2016  
Primary Completion Date: September 2012 (Final data collection date for primary outcome measure)

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
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</table>
| **Experimental: ARM A - ATO/ATRA** | Drug: arsenic trioxide  
Induction Arsenic Trioxide (As2O3=ATO), 0.15 mg/Kg IV over 2 hours daily starting on day 1. ATO will be continued until hematological CR or for a maximum of 60 days.  
Consolidation ATO, 0.15 mg/Kg IV over 2 hours daily for 5 days every week. Treatment will be continued for 4 weeks on and 4 weeks off, for a total of 4 cycles (last cycle administered on weeks 25 - 28).  
Drug: all-trans retinoic acid (ATRA)  
Induction All-trans retinoic acid (ATRA), 45 mg/m²/day will be administered orally in two equally divided doses and rounded to the nearest 10 mg increment, starting on day 1. ATRA treatment will be continued until hematological complete remission (CR, see below for definition) or for a maximum of 60 days.  
Consolidation ATRA, 45 mg/m²/day will be administered orally in two equally divided doses and rounded to the nearest 10 mg increment. Treatment will be administered for 2 weeks on 2 weeks off and for a total of 7 cycles (last cycle administered on weeks 25 - 26). |
| **Active Comparator: ARM B - ATRA** | Drug: idarubicin  
Induction  
Idarubicin, 12 mg/m² on days 2, 4, 6 and 8 by short (20') intravenous infusion.  
If no hematological CR is achieved by 60 days after start of induction, patient will go off-study.  
Consolidation  
1st cycle Idarubicin, 5 mg/m²/day by short (20') intravenous infusion on days 1, 2, 3, 4.  
3rd cycle Idarubicin, 12 mg/m²/day as short (20') intravenous infusion only on day 1.  
Drug: mercaptopurine  
Maintenance therapy 6-Mercaptopurine (6-MP), 50 mg/m²/day orally. The dose will be adjusted according to hematopoietic toxicity during the follow-up period  
Drug: methotrexate  
Maintenance therapy Methotrexate (MTX), 15 mg/m²/weekly intramuscularly. The dose will be adjusted according to toxicity during the follow-up period.  
Drug: all-trans retinoic acid  
Induction ATRA, 45 mg/m²/day will be administered orally in two equally divided doses and rounded to the nearest 10 mg increment, starting on day 1. ATRA treatment will be continued until hematological CR and for a maximum of 60 days.  
Consolidation  
1. 1st cycle ATRA, 45 mg/m²/day, will be administered orally in two equally divided doses and rounded to the nearest 10 mg increment, starting from day 1 to day 15.  
2. 2nd cycle ATRA, 45 mg/m²/day will be administered orally in two equally divided doses and rounded to the nearest 10 mg increment, starting from day 1 to day 15.  
3. 3rd cycle ATRA, 45 mg/m²/day will be administered orally in two equally divided doses and rounded to the nearest 10 mg increment, starting from day 1 to day 15.  
Maintenance therapy  
ATRA, 45 mg/m²/day orally, for 15 days every three months until a two year period is completed. |

**Detailed Description:**
- Arm I:  
  - Induction therapy: Patients receive oral tretinoin twice daily and arsenic trioxide IV over 2 hours on days 1-60. Patients achieving hematological complete remission go on to receive consolidation therapy.  
  - Consolidation therapy: Patients receive oral tretinoin twice daily on days 1-14. Treatment with tretinoin repeats every 4 weeks for up to 7...
courses. Patients also receive arsenic trioxide IV over 2 hours on days 1-5 in weeks 1-4. Treatment with arsenic trioxide repeats every 8 weeks for up to 4 courses.

Arm II:

- Induction therapy: Patients receive tretinoin as in arm I induction therapy and idarubicin IV over 20 minutes on days 2, 4, 6, and 8. Patients achieving hematological complete remission go on to receive consolidation therapy.
- Consolidation therapy: Patients receive oral tretinoin twice daily on days 1-45, idarubicin IV over 20 minutes on days 1-4 and day 31, and mitoxantrone hydrochloride IV over 30 minutes on days 16-20.

Marrow samples are collected after completion of consolidation therapy and analyzed by reverse transcriptase-PCR for molecular remission. Patients achieving molecular remission (PML-RARA negative) go on to receive maintenance therapy.

- Maintenance therapy: Patients receive oral mercaptopurine once daily and methotrexate intramuscularly once weekly for 3 months. Treatment with mercaptopurine and methotrexate repeats every 3 months for 7 courses. After completion of course 1 of mercaptopurine and methotrexate, patients receive oral tretinoin once daily on days 1-15*. Treatment with tretinoin repeats every 3 months for 6 courses.

NOTE: *Patients do not receive mercaptopurine and methotrexate during tretinoin administration.

After completion of study therapy, patients are followed periodically for 5 years.

As of 14th September 2010, all patients needed to evaluate the primary endpoint (162 patients) have been recruited but the trial accrual continued in order to assess one secondary outcome (QoL).”

Criteria

Inclusion criteria

- Signed written informed consent according to IGH/EU/GCP and national local laws
- Newly diagnosed APL by cytomorphology, confirmed also by molecular analysis*
- Age ≤ 71 years
- WHO performance status 0 -2 included
- WBC at diagnosis ≤ 10 x 10^9/L
- Serum total bilirubin ≤ 3.0 mg/dL (≤ 51µmol/L)
- Serum creatinine ≤ 3.0 mg/dL (≤ 260 µmol/L)

The confirmation of diagnosis at genetic level (microspeckled PML nuclear distribution by PGM3 monoclonal antibody and/or PML/RARa fusion by RT-PCR and/or demonstration of t(15;17) by karyotyping) will be mandatory for patient eligibility. However, in order to avoid delay in treatment initiation, patients can be randomised on the basis of morphologic diagnosis only and before the results of genetic tests are available.

Exclusion criteria

- Age < 18 and ≥ 71
- WBC at diagnosis > 10 x 10^9/L
- Other active malignancy at time of study entry
- Lack of diagnostic confirmation at genetic level
- Significant arrhythmias, EKG abnormalities (*see below) or neuropathy
- Other cardiac contraindications for intensive chemotherapy (L-VEF <50%)
- Uncontrolled, life-threatening infections
- Severe non-controlled pulmonary or cardiac disease
- Women who are either pregnant or breast feeding, or of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they meet one of the following definitions:
  - Amenorrhea;
  - post surgical bilateral oophorectomy with or without hysterectomy;
  - using a highly effective method of birth control (defined as those which result in a failure rate less than 1% per year) when used consistently and correctly such as implants, injectables, oral contraceptives, IUDs, sexual abstinence or vasectomized partner.
- Concomitant severe psychiatric disorder
- HIV positivity

*EKG abnormalities:
  - Congenital long QT syndrome;
  - History or presence of significant ventricular or atrial tachyarrhythmia
  - Clinically significant resting bradycardia (<50 beats per minute)
  - QTc > 450 msec on screening EKG (using the QTcF formula detailed on page 18)
  - Right bundle branch block plus left anterior hemiblock, bifascicular block
Use of other investigational drugs at the time of enrolment or within 30 days before study entry

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT00482833

Show 110 Study Locations

Sponsors and Collaborators

Gruppo Italiano Malattie EMatologiche dell'Adulto

Study Alliance Leukemia (SAL) Group

Investigators

Study Chair: Francesco Lo Coco, MD Azienda Ospedaliera Universitaria Policlinico Tor Vergata

More Information

Additional Information:

Clinical trial summary from the National Cancer Institute's PDQ® database

GIMEMA Foundation Website

No publications provided

Responsible Party: Gruppo Italiano Malattie EMatologiche dell'Adulto

ClinicalTrials.gov Identifier: NCT00482833

History of Changes

Other Study ID Numbers: APL0406, GIMEMA-SAL-APL0406, EUDRACT-2006-006188-22

Study First Received: June 4, 2007

Last Updated: January 10, 2013

Health Authority: Italy: Ethics Committee

Keywords provided by Gruppo Italiano Malattie EMatologiche dell'Adulto:

adult acute promyelocytic leukemia (M3)
adult acute myeloid leukemia with t(15;17)(q22;q12)
untreated adult acute myeloid leukemia

Additional relevant MeSH terms:

Leukemia
Leukemia, Promyelocytic, Acute
Neoplasms by Histologic Type
Neoplasms
Leukemia, Myeloid, Acute
Leukemia, Myeloid
6-Mercaptopurine
Methotrexate
Arsenic trioxide
Idarubicin
Tretinoin
Antimetabolites
Molecular Mechanisms of Pharmacological Action
Pharmacologic Actions
Antimetabolites, Antineoplastic

Antineoplastic Agents
Therapeutic Uses
Immunosuppressive Agents
Immunologic Factors
Physiological Effects of Drugs
Nucleic Acid Synthesis Inhibitors
Enzyme Inhibitors
Antibiotics, Antineoplastic
Abortifacient Agents, Nonsteroidal
Abortifacient Agents
Reproductive Control Agents
Dermatologic Agents
Folic Acid Antagonists
Antirheumatic Agents
Keratolytic Agents

ClinicalTrials.gov processed this record on February 06, 2013