PETHEMA/HOVON

Treatment of Acute Promyelocytic Leukemia

PETHEMA LPA 2005/HOVON 79 APL

Remission Induction with ATRA + Idarubicin. Risk-adapted consolidation with ATRA and Anthracycline-based Chemotherapy (Idarubicin/Mitoxantrone) with Addition of Ara-C for High-risk Patients. Maintenance Therapy with ATRA + Low Dose Chemotherapy (Methotrexate + Mercaptopurine)

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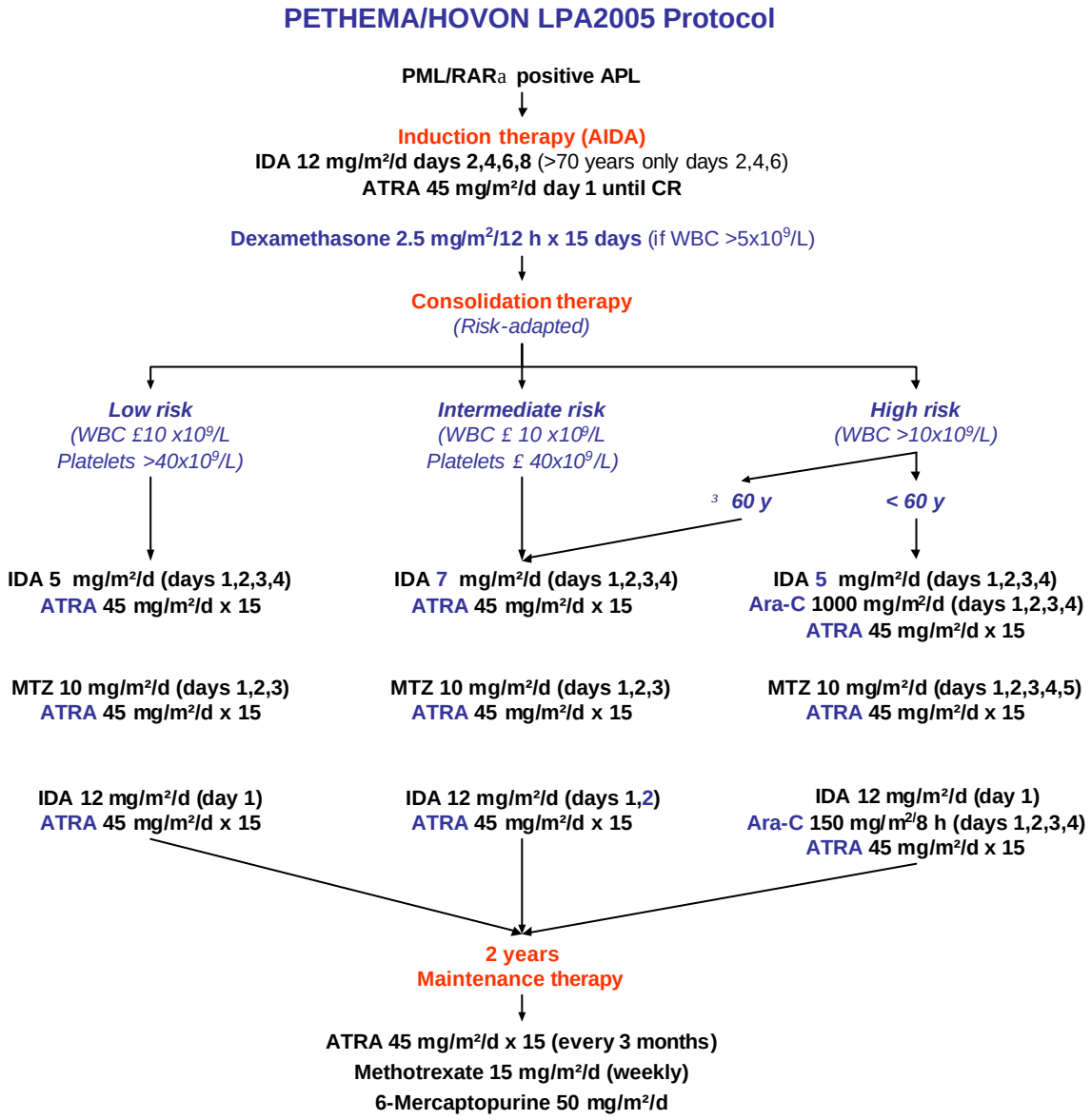
SYNOPSIS

Study phase	Phase II
Study objectives	To assess antileukemic efficacy and toxicities of a risk-adapted strategy in patients with APL treated with the combination of ATRA and anthracycline-based chemotherapy using idarubicin for induction and consolidation and the addition of ara-C in consolidation for high-risk patients.
Patient population	Patients with genetic diagnosis of acute promyelocytic leukemia
Study design	Prospective, multicenter, non-randomised phase II study.
Phases and duration of treatment	Induction therapy with simultaneous ATRA (45 mg/m^2 day until CR) and idarubicin (12 mg/m^2 day on days 2, 4, 6 and 8), 3 monthly consolidation courses with ATRA (45 mg/m^2 days 1–15) and idarubicin (5 mg/m^2 days 1–4) for course 1, mitoxantrone (10 mg/m^2 days 1–3) for course 2 and idarubicin (12 mg/m^2 day 1) for course 3. Consolidation was reinforced for intermediate-risk patients by increasing idarubicin to 7 mg in course 1 and to 2 days in course 3. For high-risk patients, consolidation was reinforced with the addition of ara-C in courses 1 and 3. Maintenance therapy with ATRA and low dose chemotherapy with methotrexate and 6-mercaptopurrine is scheduled for two years
Number of patients	300
Adverse events	Adverse events will be documented if observed, mentioned during open questioning, or when spontaneously reported
Planned start of recruitment	April 2006
Planned end of recruitment	2008

SCHEMA



Note: In patients aged <20 years, the ATRA dose will be reduced to 25 mg/m²/day fractionated into 2 doses.

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1. BACKGROUND AND RATIONALE

The current recommendations for treatment of patients with newly diagnosed acute promyelocytic leukemia (APL) include all-*trans*-retinoic acid (ATRA) and anthracycline-based chemotherapy for remission induction, anthracycline-based chemotherapy for consolidation, and ATRA with low dose chemotherapy for maintenance.[1-3] Using ATRA and anthracycline monochemotherapy (LPA96 study),[4] the Spanish cooperative group PETHEMA first reported outcome results similar to those obtained in other studies using ATRA with anthracycline-based chemotherapy combinations.[5-10] Aiming to improve the antileukemic efficacy, a new trial based on a risk-adapted strategy was started in 1999 (LPA99 study). In this study, intermediate- and high-risk patients (as previously defined[11]) received ATRA during consolidation therapy in combination with moderately reinforced anthraycline monochemotherapy. Recently, the PETHEMA group has reported the results obtained in 251 consecutive patients with newly diagnosed PML/RARa positive APL who had been enrolled in the LPA99 study. Results of the latter protocol were compared with the updated results of 175 patients who were enrolled in the LPA96 study.[12] The main conclusions in that study were: i) Induction results in both the LPA96 and LPA99 studies confirmed the virtual absence of leukemia resistance using ATRA and idarubicin treatment alone (AIDA regimen); ii) The reinforced consolidation therapy for intermediate- and high-risk patients certainly caused a significant improvement of the antileukemic efficacy in these settings; and iii) The increased doses of idarubicin and the addition of ATRA in the three cycles of consolidation therapy, although increased moderately the hematological toxicity, maintained a high degree of treatment compliance without increasing toxic deaths.

Once most of the objectives of the currently ongoing PETHEMA LPA99 study have been achieved after enrolling more than 500 patients with APL, and based on the above outlined conclusions, a new study (LPA2005) has been designed taking into account the following considerations:

1. For induction therapy, no essentials changes in the AIDA regimen have been made. However, because of the unfavorable impact of several risk factors observed on the occurrence of lethal hemorrhage (age, > 70 years; hyperleukocitosis, greater than 10 x 10^9L; and abnormal creatinine, > 1.4 mg/dL), a reinforcement of platelet transfusion policy to achieve more than 50 x 10^9L is proposed for patients presenting any of these risk factors.
2. For consolidation therapy, a risk-adapted strategy based on the combination of ATRA and anthracycline monochemotherapy has been maintained as backbone, except for high-risk patients (defined by hyperleucocytosis higher than 10×10^9/L).
    a. The low relapse rate observed in low- and intermediate-risk patients recommends being extremely prudent for any change in these settings. A slight reduction of mitoxantrone in the second consolidation course and the addition of ATRA to the 3 consolidation courses have been proposed.
    b. The still unsatisfactory relapse rate observed in high-risk patients has induced to reinforce consolidation chemotherapy with the addition of ara-C to the idarubicin courses. This option was based on the results recently reported by the Italian GIMEMA group in high-risk patients

younger than 60 years.[13] A 4-year relapse rate of 3% was obtained with the addition of ATRA to consolidation courses with anthracycline-based chemotherapy combinations as used in the original AIDA0493 study.

3. Once demonstrated the benefit of this therapeutic phase in two randomized studies,[5,9] no substantial changes should be made for maintenance therapy.

The expected improvements of these changes in the treatment compared to the LPA99 treatment are small and probably only present for a subgroup of patients, ie for patients with risk factors for lethal hemorrhage or patients with high risk for relapse. To demonstrate such improvements with a randomized study would require a very large number of patients (in subgroups), and such a study would be unfeasible. Therefore a single arm non-randomized study design has been chosen with continuation of international collaboration, the same APL treatment in all participating hospitals and registration of all patient data in the central study database. The results in this study will be compared with the results obtained in the LPA99 (and LPA96).

2. STUDY OBJECTIVES

2.1. Primary objectives

- To evaluate the efficacy and toxicity of a risk-adapted protocol that use idarubicin for induction and consolidation therapy in patients with APL.
- To evaluate the impact of mitoxantrone reduction on the event-free, disease-free, and overall survival, as well as on the duration of remission and cumulative incidence of relapse in low- and intermediate-risk patients with APL.
- To evaluate the impact of the addition of ara-C to idarubicin courses of consolidation for high-risk patients (administered as in the original GIMEMA protocols) on the event-free, disease-free, and overall survival, as well as on the duration of remission and cumulative incidence of relapse.
- To evaluate the toxicity of the induction, consolidation, and maintenance chemotherapy in the whole series and in each treatment group in patients with APL.

2.2. Secondary objectives

- To compare all outcomes with those achieved with the PETHEMA LPA99 protocol.

3. SELECTION OF PATIENTS

Eligibility criteria are patient-specific criteria. The only explicit eligibility criteria on this study are defined below. These criteria may not be waived by the study chair and will be reviewed in case of an audit.

3.1. Inclusion criteria

- Age 18-75 years
- ECOG performance status = 3.
- Morphological diagnosis of APL (FAB-M3 or M3 variant). Those cases without typical morphology but with PML-RARα rearrangement should also be included.
- Genetic diagnosis: t(15;17) demonstrated by conventional karyotyping, a PML-RARα rearrangement detected by RT-PCR or FISH, microspeckled PML protein pattern demonstrated by PG-M3 monoclonal antibody. Obviously, the result of these tests may become available after having initiated the treatment based on a tentative morphological diagnosis.

3.2. Exclusion criteria

- Age >75 years (the treatment with this protocol can be considered on an individual basis)
- Absence of PML-RARα rearrangement.
- The patient must not have received any systemic definitive treatment for APL, including cytotoxic chemotherapy or retinoids. Prior therapy with corticosteroids, hydroxiurea or leukapheresis will not exclude the patient.
- Prior chemotherapy or radiotherapy for the treatment of prior malignancy.
- Presence of an associated neoplasm.
- Presence of a severe psychiatric disease.
- HIV seropositivity.
- Contraindication for intensive chemotherapy, especially to anthracyclines.
- Serum creatinine = 250 µmol/l (= 2.5 mg/dL)
- Bilirubin, alkaline phosphatase, or SGOT > 3 times the upper normal limit
- Positive pregnancy test.

[a] The presence of secondary cytogenetic changes associated with t(15;17) is not a reason for exclusion nor do they require a different therapeutic approach.

4. REGISTRATION REQUIREMENTS

4.1. Informed Consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, alternatives, potential benefit, side-effects, risks and discomforts. Human protection committee approval of this protocol and a consent form is required.

4.2. Cytogenetic Studies

Sample collection before treatment is mandatory and should be performed on leukemia cells from bone marrow. The results of the cytogenetic studies do not necessarily need to be known prior to initiate therapy. For details of cytogenetic characterization, see Section 5.

4.3. FISH and Molecular Studies

Collection of on-study bone marrow and peripheral blood samples for molecular analysis is mandatory. The results of these studies do not necessarily need to be known prior to initiate therapy. See Section 5 for sample requirements, sample shipment instructions and protocols for FISH and RT-PCR.

4.4. Immunostaining with Monoclonal Antibodies

Bone marrow and peripheral blood dry (uncolored) smears should be collected for immunofluorescence studies with the PG-M3 anti-PML monoclonal antibody. See Section 5 for details on the protocol for PML immunostaining.

5. DIAGNOSTIC STUDIES, SHIPMENT AND SAMPLE BANKING

5.1. Laboratory studies

5.1.1. Sample centralization and banking

- 3-4 bone marrow smears and 3-4 peripheral blood smears. Shipment to NRL can be done at room T. Smears will be used for PML staining pattern or stored for banking at -20 °C covered by aluminum paper.
- One bone marrow (BM) aspirate vial (1-2 ml) in sodium citrate. One peripheral blood (PB) vial (5-20 ml) in sodium citrate. Shipment to NRL is recommended by overnight. courier at 4 °C. Samples will be used for RNA extraction and RT-PCR analysis of PML/RARα. Isolated mononuclear cells in guanidium isotiocyanate (GTC) will be stored for banking at – 20 °C.
- Bone marrow aspirate (1-2 ml) will be collected in 6 ml of heparinised RPMI (with FCS and antibiotics) and shipped at room T for karyotypic and FISH studies. Samples will be processed at arrival for these diagnostic studies (see below) and pelleted nuclei fixed with methanol and acetic acid (3:1) will be stored at – 20 °C.

5.1.2. Conventional karyotyping.

Conventional karyotyping on G-banded metaphases obtained from BM samples will be carried out using conventional methods. It is strongly recommended that karyotypic analysis is done on 24 hrs and 48 hrs cultures.

5.1.3. FISH analysis of PML/RARa

FISH will be carried out using standard methods and commercially available fluorescently labelled probes. Although in some cases PB samples are amenable for study (in particular when hyperleucocytosis is present at diagnosis), FISH is preferably performed in BM samples. The protocol for FISH detection of PML/RARa is reported in details in ref. 14

5.1.4. RT-PCR analysis of PML/RARa

RT-PCR analysis will be carried out preferably on RNA extracted from BM. The protocol to be adopted for RT-PCR analysis of PML/RARa is the one designed by the Biomed-1 Concerted Action.[15]

5.1.5. Immunostaining with anti-PML

The staining pattern of the PML protein will be analyzed using indirect fluorescence and the monoclonal antibody PGM3 in diagnostic BM smears. The detailed protocol is reported in ref. 16 and 17.

6. PATIENT REGISTRATION AND DATA SUBMISSION

Although treatment with ATRA alone is permitted during the diagnostic process, prior to registration, patients should be registered before starting chemotherapy (idarubicin). Nevertheless, registration can be also done within three working days after starting the protocol treatment. To avoid selection bias, **all** patients with a diagnosis of APL must be registered, regardless they are eligible for the study.

6.1. Registration

HOVON participants register patients at the HOVON Data Center of the Erasmus MC - Daniel den Hoed by phone call: +31.10.4391568 or fax +31.10.4391028 Monday through Friday, from 09:00 to 17:00, or via the Internet through TOP (Trial Online Process; https://www.hdc.hovon.nl/top). A logon to TOP can be requested at the HOVON Data Center for participants. Each patient will be given a unique patient study number, which will be given immediately by TOP or phone and confirmed by fax or email.

PETHEMA participants register patients at the PETHEMA Data Center (Servicio de Hematología. Hospital Universitario La Fe. Avda Campanar 21. 46009 Valencia, Spain) by Fax +34-96-197 3057 or by e-mail msanz@uv.es by mean of a specific registration form.

6.2. Requested Information for Registration

The following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
  - Investigator's fax number (if possible)
  - Investigator's e-mail address
- Patient Identification
  - Patient's initials and chart number
  - Patient demographics
  - Sex
  - Birth date (dd/mm/yyyy)
  - Zip code of residence

- Eligibility Verification

  Patients must meet all of the eligibility requirements listed in Section 3.0. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the Coordinating Center.

- Informed consent

  Patient must provide signed and dated written informed consent. Patients must understand risks and benefits of this treatment.

- Instructions for Patients who Do Not Start Protocol Treatment

  If a patient with APL and registered in this study does not receive the protocol treatment the registration form will be filled in with reason for not starting protocol treatment and the patient will be registered in TOP (6.1).

6.3. Data submission

The CRF's that must be submitted to the Data Management Center (See Section 6) are the following:

- Patient registration form: complete and submit within 3 days of registration (Appendix II).
- Data at diagnosis form: complete and submit within 7 days of registration (Appendix III).
- Induction therapy form: complete and submit within 7 days after completion of the induction therapy (Appendix IV).
- Consolidation therapy form: complete and submit within 7 days after completion of each cycle of consolidation therapy (Appendix V).
- Maintenance therapy form: submit this form every 3 months (every ATRA maintenance course) after the start of maintenance therapy for 2 years (Appendix VI).
- Follow up form: submit this form every 6 months (Appendix VII).
- Relapse form: complete and submit in case of relapse.
- Serious adverse event (SAE) form: Expedited reports are to be submitted using SAE form (Appendix VIII) within 5 working days when the SAE is graded greater than 3 (see Section 11).

The CRF's are available both in paper form, and as Word document with boxes that can be filled out. The patient data should preferably be entered in Word, and sent by email directly to Valencia and copied to HOVON Data Center (for paper form and Word document).

7. TREATMENT PROTOCOL

7.1. Induction Therapy

7.1.1. Chemotherapy

All-trans retinoic acid, will be administered PO from the first day at a dose of 45 mg/m²/day ("rounded" up to the nearest 10 mg for adults), fractionated into 2 doses.

- In patients aged <20 years**,** the ATRA dose will be reduced to 25 mg/m²/day (round to the nearest 10 mg, not necessarily up to the nearest 10 mg) fractionated into 2 doses.

- The treatment with ATRA will continue until a CR is achieved or for a maximum of 90 days in the case of persistence of atypical promyelocytes in the bone marrow.

Idarubicin, 12 mg/m² on days 2, 4, 6 and 8 of treatment by intravenous infusion (2-5 minutes).

- In patients older than 70 years of age only 3 doses of idarubicin will be given on days 2, 4, and 6.

7.1.2. Supportive Measures

Dexamethasone, 2.5 mg/m^2/12h days 1 to 15 for patients with WBC more than $5x10^9$/L at presentation. Dexamethasone at the same dose should be also started in patients who achieve WBC more than $5x10^9$/L during the 2 first weeks of differentiation therapy. In this case, dexamethasone should be administered during 15 days from starting. No prophylaxis with dexamethasone should be given for the remaining patients.

Transfusion of platelet concentrates to keep up counts above 30x109/L during the first 10 days and PRC to maintain hemoglobin levels > 5.5 µmol/l (9 g/dl). For patients with high risk of lethal hemorrahage (age, > 70 years; hyperleukocytosis, greater than 10 x 10^9/l or abnormal creatinine, > 140 µmol/l or > 1.4 mg/dL), platelet transfusion should be given for achieving more than 50 x 109/l.

Heparin and antifibrinolytics (e-aminocaproic acid and its analogue, tranexamic acid) are not recommended as prophylaxis.

7.1.3. Dose Modifications for Induction Therapy

7.1.3.1. Dose Modification for idarubicin during Induction

In case of hepatotoxicity with a bilirubin greater than 80 µmol/l (3.0 mg/dl) modification of idarubicin dosage should be made reduce to give 75% of dose.

7.1.3.2. Dose Modification for ATRA during Induction

The treatment with ATRA may be withdrawn temporarily if the following complications arise:

ATRA syndrome: In the event of respiratory distress, pulmonary infiltrates, pleural or pericardial effusion, hypoxemia, hypotension, peripheral edemas or weight gain, with or without hyperleukocytosis and other causes that suggest the presence of an ATRA syndrome. In this case the following measures should be taken immediately:

- **Temporary withdrawal** of ATRA.
- **Dexamethasone**, 10 mg/12 h IV until resolution of the event.
- In some cases it may be necessary to administer **furosemide**.

Pseudotumor cerebri: In the event of severe headaches with nausea, vomiting, and visual disorders, especially in pediatric ages, it is often necessary to temporarily discontinue the ATRA and to treat with opiates.

Hepatotoxicity: An increase in serum bilirubin, SGOT/SGPT, or alkaline phosphatase to 5 times the normal level requires a temporary withdrawal of ATRA.

7.2. Consolidation therapy

Once hematological recovery is achieved (absolute neutrophil count >1.5x10^9/l and platelet count >100x10^9/l), patients who achieve CR will undergo three successive courses of consolidation chemotherapy in a monthly schedule if hematological recovery between cycles allows this.

The therapeutic consolidation strategy varies in function of the relapse risk group.

7.2.1. Low-risk patients

This group includes patients with a leukocyte count lower than or equal 10 x 10^9/L and a platelet count greater than 40 x 10^9/L at presentation.

7.2.1.1. First consolidation course

Idarubicin, 5 mg/m²/d by intravenous infusion (2-5 minutes) on days 1, 2, 3, 4.

ATRA, 45 mg//m²/d PO fractionated into 2 doses on days 1 to 15. In patients aged <20 years, the ATRA dose will be reduced to 25 mg/m²/day fractionated into 2 doses.

7.2.1.2. Second consolidation course

Mitoxantrone, 10 mg/m²/d by quick intravenous infusion (2-5 minutes) on days 1, 2, 3.

ATRA, 45 mg/m²/d PO fractionated into 2 doses on days 1 to 15. In patients aged <20 years, the ATRA dose will be reduced to 25 mg/m²/day fractionated into 2 doses.

7.2.1.3. Third consolidation course

Idarubicin, 12 mg/m²/d by intravenous infusion (2-5 minutes) only one day.

ATRA, 45 mg//m²/d PO fractionated into 2 doses on days 1 to 15. In patients aged <20 years, the ATRA dose will be reduced to 25 mg/m²/day fractionated into 2 doses.

7.2.2. Intermediate-risk patients

The intermediate risk group includes patients with a leukocyte count lower than or equal to 10 x 10^9/L and platelets count lower than or equal to 40 x 10^9/L at presentation.

7.2.2.1. First consolidation course

Idarubicin, 7 mg/m²/d by intravenous infusion (2-5 minutes) on days 1, 2, 3 and 4.

ATRA, 45 mg/m²/d PO fractionated into 2 doses on days 1 to 15. In patients aged <20 years, the ATRA dose will be reduced to 25 mg/m²/day fractionated into 2 doses.

7.2.2.2. Second consolidation course

Mitoxantrone, 10 mg/m²/d by quick intravenous infusion (2-5 minutes) on days 1, 2, 3.

ATRA, 45 mg/m²/d PO fractionated into 2 doses on days 1 to 15.

7.2.2.3. Third consolidation course

Idarubicin, 12 mg/m²/d by intravenous infusion (2-5 minutes) on days 1, 2.

ATRA, 45 mg/m²/d PO fractionated into 2 doses on days 1 to 15. In patients aged <20 years, the ATRA dose will be reduced to 25 mg/m²/day fractionated into 2 doses.

7.2.3. High-risk patients younger than 60 year

The high risk group includes patients with a leukocyte count greater than 10 x 10^9/L, regardless of the platelet count at presentation.

7.2.3.1. First consolidation course

Idarubicin, 5 mg/m²/d by intravenous infusion (2-5 minutes) on days 1, 2, 3, 4.

Ara-C, 1000 mg/m²/d by 6h intravenous infusion on days 1, 2, 3, 4.

ATRA, 45 mg/m²/d PO fractionated into 2 doses on days 1 to 15. In patients aged <20 years, the ATRA dose will be reduced to 25 mg/m²/day fractionated into 2 doses.

7.2.3.2. Second consolidation course

Mitoxantrone, 10 mg/m²/d by quick intravenous infusion (2-5 minutes) on days 1, 2, 3, 4, 5.

ATRA, 45 mg/m²/d PO fractionated into 2 doses on days 1 to 15. In patients aged <20 years, the ATRA dose will be reduced to 25 mg/m²/day fractionated into 2 doses.

7.2.3.3. Third consolidation course

Idarubicin, 12 mg/m²/d by intravenous infusion (2-5 minutes) on day 1.

Ara-C, 150 mg/m²/8h subcutaneous on days 1, 2, 3, 4.

ATRA, 45 mg/m²/d PO fractionated into 2 doses on days 1 to 15. In patients aged <20 years, the ATRA dose will be reduced to 25 mg/m²/day fractionated into 2 doses.

7.2.4. High-risk patients older than 60 year

These patients should be treated like intermediate-risk patients (see section 6.2.2).

7.3. Maintenance therapy

6-Mercaptopurine, 50 mg/m²/day orally, beginning one month after hematological recovery of the final consolidation. The dose will be adjusted on subsequent controls in all cases. This treatment must be continued for two years.

Methotrexate, 15 mg/m²/weekly intramuscularly or orally, beginning one month after hematological recovery of the last consolidation. This treatment must be continued for two years.

ATRA, 45 mg/m²/day orally, for 15 days every three months until the completion of a 2-year period. In patients aged <20 years, the ATRA dose will be reduced to 25 mg/m²/day fractionated into 2 doses. The first ATRA maintenance course will begin three months after completing the third consolidation. During the days on which ATRA is administered, the treatment with MTX and 6-MP will be discontinued.

7.3.1. Dose Modifications for maintenance treatment

The doses of methotrexate and 6-mercaptopurine will be modified as a function of the peripheral blood counts:

- Absolute neutrophil count (ANC) between 1 and 1.5 x 10^9/L: Reduce the dose by a half.
- ANC <1 x 10^9/L: Suspend maintenance temporarily.

8. CRITERIA FOR RESPONSE AND RELAPSE

The assessment of response after treatment for acute leukemia requires a physical examination, complete blood count, platelet count, differential count, and bone marrow aspiration and biopsy. Extramedullary sites known to be involved by leukemia prior to treatment (e.g., mediastinal lymphadenopathy or CSF) must be reexamined as well. Immunophenotyping, cytochemistry, and cytogenetic analyses are supportive date but are not required for clinical assessment. Investigators are cautioned that the bone marrow cytology and peripheral blood differential count in patients who are recovering from chemotherapy or who have received hematopoietic growth factors or cytokines may be shifted to immaturity, reflecting regenerating hematopoiesis; this should not be misinterpreted as residual or recurrent leukemia. Whenever the initial morphological result is ambiguous, a second bone marrow examination should be performed = one week later, and confirmatory data should be gathered from cytogenetic analyses, inmunophenotyping, or cytochemistry.

8.1. Complete Remission (CR)

Requires all of the following:

- Peripheral Blood Counts
  - Absolute neutrophil count >1.5x10^9/l
  - Platelet count > 100x10^9/l
  - No leukemic blasts or promyelocytes in the peripheral blood.
- Bone Marrow
  - Cellularity of bone marrox biopsy or clot section >20% with maturation of all cell lines
  - < 5% blasts or malignant promyelocytes
- No extramedullary leukemia, such as CNS or soft tissue involvement.

8.2. Treatment Failure

8.2.1. Treatment Failure due to resistant disease

This type of failure is not expected to occur with this protocol. In case of suspecting resistance, it should be notified the Study Chair before making therapeutic decisions based on this observation[b].

[b] Morphological features in BM aspirates performed early during induction therapy may lead to erroneously labeling as resistant some individual patients showing delayed maturation features and/or persistence of atypical promyelocytes. These findings, which are occasionally detectable several weeks after the start of treatment (up to 40-50 days), should in no way lead to therapeutical changes. Treatment should be continued until terminal differentiation of blasts and achievement of CR that invariably occurs in all patients with genetically proven APL who survive after ATRA-based induction.

8.2.2. Treatment Failure due to death of the patient:

Patient died between the first day of induction therapy and before CR is documented.

8.3. Relapse

Relapse following complete remission is defined as:

8.3.1. Hematological relapse:

> 5% blasts/promyelocytes in the bone marrow. If the bone marrow contains 6% to 20% blasts/promyelocytes, then a bone marrow performed 1 week later documenting more than 5% blasts is necessary to meet the criteria for relapse. Genetic confirmation should be performed with any of the methods described in Sections 4 and 5.

8.3.2. Extramedullary relapse:

Documentation in skin, CSF, or other site required. Genetic confirmation should be performed with any of the methods described in Sections 4 and 5.

8.3.3. Molecular relapse:

It is defined as the reappearance of PCR positivity in 2 consecutive bone marrow samples at any time after consolidation therapy. PCR positivity is defined as the reappearance on an ethidium bromide gel of the PML/RARα-specific band visualized at diagnosis, using an RT-PCR assay with a sensitivity level of 10^{-4}. A positive PML/RARα by RT-PCR at the end of consolidation (molecular persistence) and at any time during follow up (molecular relapse) must always be confirmed in a new BM sample collected within the next 2 weeks and sent to one National Reference Laboratory.

9. REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

- Failure to achieve CR after completion of induction chemotherapy (ATRA + idarubicin).

- Failure to achieve molecular remission after completion of consolidation chemotherapy (molecular persistence). As for molecular relapse (see 8.3.3),a positive PML/RARα by RT-PCR at the end of consolidation must be confirmed with a low sensitivity method in a new BM sample collected within 2 weeks and sent to the National Reference Laboratory.. If it is positive, it has to be confirmed by reference laboratories. Patients with confirmed molecular persistence or molecular relapse will be removed from protocol.

- Relapse as defined in 8.3.

- In the event that a patient begins therapy not defined in this protocol, patients should be followed for relapse or progression, secondary malignancy, and survival.

- Extraordinary medical circumstances: If, at any time the constraints of this protocol are detrimental to the patient´s health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:
  - Document the reason(s) for discontinuation of therapy in patient records.
  - Notify the Study Chair.

10. CLINICAL AND ANALYTICAL MONITORING

Tests & Observations	Prior to Study	Induction	Prior to Each Consolidation Cycle			During Each Consolidation Cycle			Prior to and During Maintenance	Follow-Up*
			C1	C2	C3	C1	C2	C3		
History/Physical exam	X	Daily	X	X	X	Wk	Wk	Wk	Monthly	X
Height/Weight/BSA	X	Daily	X	X	X	Wk	Wk	Wk		X
Performance status**	X		X	X	X	Wk	Wk	Wk	Monthly	X
Pregnancy test***	X									
Blood counts	X	3x/Wk+	X	X	X	Wk	Wk	Wk	Monthly	X
Prothrombin time, APTT, Thrombin time, Fibrinogen and PDF or PDX or D dimmers	X	3x/Wk+								
Serum biochemistry: Glucose, Creatinine, Uric Acid, Bilirubin, Alkaline Phosphatase, LDH, AST, ALT, electrolytes, Calcium, Phosphorus	X	3x/Wk+	X	X	X	Wk	Wk	Wk	Monthly	PRN
Cholesterol, Triglycerides, Total Proteins, and Albumin	X	Weekly	X	X	X				Monthly	
LVEF (Echo or MUGA) (optional)	X		X						A	A
Bone Marrow Aspirate	X	B	X					D	X	X
Karyotype	X	C								
RT-PCR	X	C						D	E	E
Immunophenotype	X									

* Every 2 months for 2 years, then every 3 months for 1 year, then every 6 months for 2 years, and then as clinically indicated by alteration in peripheral blood counts.

** WHO system of assessment

*** In women with reproductive potential

X To be done

+ Daily during the first 1-2 weeks

A Prior to maintenance, then repeated yearly for 10 years.

B The first needle aspiration will be done when clear signs of recovery are observed in blood counts and peripheral blood criteria for CR are met, but never before the day 30 after ending chemotherapy, and repeated q 1-2 weeks until bone marrow criteria for CR are met. Bone marrow aspirates performed early after induction therapy usually reveal a relatively hypercellular pattern which reflects initial differentiation of leukemic cells. This finding may lead to erroneously labeling as resistant some individual patients showing delayed maturation features and/or persistence of atypical promyelocytes. These cytomorphological features, which are occasionally detectable several weeks after the start of treatment (up to 40-50 days), should in no way lead to therapeutical changes. Treatment should be continued until terminal differentiation of blasts and achievement of CR that invariably occurs in all patients with genetically proven APL who survive after ATRA-based induction.

C Early molecular and cytogentic evaluation performed after induction can be also misleading and are not informative with respect to successive outcome. Early laboratory evaluation of MRD after ATRA-based induction should only be part of investigational studies and clinicians should refrain from making therapeutic decisions based on these results.

D At the end of the third consolidation cycle

E Only for high-risk patients: every 2 months for the first semester, then every 3 months until completing 2 years, and then every 6 months for 2 years.

PRN As clinically indicated

11. SAFETY EVALUATIONS AND ADVERSE EVENTS REPORTING

11.1. Reporting Requirements for Regimens Containing Only Commercial Agents.

Expedited reporting for adverse events attributable to commercial agents (ATRA, idarubicin, ara-C, mitoxantrone, methotrexate, 6-mercaptopurine) is required as described in Table 11.1.

Table 11.1. Reporting requirements for treatment arms containing commercial agents only.

Phase II and III	Grade 1	Grade 2	Grade3	Grade 4	Grade 5
Expected[a]	Adverse Event Expedited Reporting **NOT** required	Adverse Event Expedited Reporting **NOT** required	Adverse Event Expedited Reporting **NOT** required	Attribution of Possible, Probable, or Definite. Adverse Event Expedited Reporting **required**.[b,c]	Attribution of Possible, Probable, or Definite. Adverse Event Expedited Reporting **required**.[b,d]
Unexpected	Adverse Event Expedited Reporting **NOT** required	Adverse Event Expedited Reporting **NOT** required	Adverse Event Expedited Reporting **NOT** required	Attribution of Possible, Probable, or Definite. Adverse Event Expedited Reporting **required**.[b]	Attribution of Possible, Probable, or Definite. Adverse Event Expedited Reporting **required**.[b,d]

a. A list of agent specific expected adverse events can be found in Section 12 (Drug Formulation and Procurement). Additional information regarding expected adverse events can be obtained from the package insert and the Physician´s Desk Reference®.

b. Expedited reports are to be submitted using SAE form within 5 working days to the Central Office.

c. Grade 4 hematosuppression does not have to be reported for agents known and expected to cause myelosuppression at the dose used.

d. This includes reporting of all deaths within 30 days of the last dose of treatment regardless of attribution.

The reporting of adverse reactions described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial. All reportable serious adverse reactions should also be forwarded to your local Institutional Review Board.

11.2. Reporting Secondary AML/MDS or Other Second Primary Cancers

All cases of new acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) or primary cancers that occur during or after protocol must be reported to IC-APL within 30 days of diagnosis, regardless of relationship to protocol treatment. Once data regarding survival and remission status are no longer required by the protocol, only second primaries thought to be related to protocol treatment should be reported. Not for use for reporting recurrence or metastatic disease. A copy of the pathology report should be sent, if available.

12. DRUG FORMULATION AND PROCUREMENT

12.1. ATRA

12.1.1. Other Names

Tretinoin, All-trans Retinoid Acid, Vesanoid.

12.1.2. Classification

Differentiation inducing agent, noncytotoxic.

12.1.3. Mode of Action

Tretinoin is a natural metabolite of retinol and belongs to a class of retinoids, which are structurally related to vitamin A and involved in regulation of various biological processes. It induces terminal differentiation in several hemopoietic precursor cell lines and in cells from patients with acute promyelocytic leukemia (APL). The exact mechanism of action is not known, but tretinoin induces maturation of leukemic cells and appearance of normal hemopoietic cells

12.1.4. Storage and Stability

The intact capsules may be stored at room temperature and protected from light.

12.1.5. Administration

Oral absorption is better with food.

12.1.6. Incompatibilities

Since drug-drug interactions may be important in altering levels of retinoids, the following medications should be avoided if possible. However, to date there are no data to suggest that these medications increase or decrease the efficacy or toxicity of ATRA.

Medications which induce the hepatic cytochrome P-450 system: Barbituates, Rifampin, Glucocorticoids.

Medications which inhibit the hepatic cytochrome P-450 system: Cimetidine, Diltiazem, Erythomycin, Ketoconazole, Verapamil, Cyclosporin.

12.1.7. Availability

Commercially available for oral use in 10 mg soft gel capsules.

12.1.8. Side Effects

The side effect of systemic retinoid therapy closely resemble those of hypervitaminosis A syndrome. A list of the known retinoids toxicities is given below.

ORGAN SITE	SIDE EFFECT	ONSET			
Dose-limiting side effects are in ***bold, italics*** I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)					
Auditory/hearing	ototoxicity (19-25%)[12,13]		E		
Blood/bone marrow febrile neutropenia	basophilia (severe, rare)[15,16]		E		
	hyperleukocytosis (75%)	I	E		
Cardiovascular (general)	pericarditis (6%)[9]		E	D	
	edema (> 25%)		E		
Coagulation	thrombosis/embolism (8%)[9]		E	D	
Constitucional symptoms	fatigue (> 25%)		E		
	fever (> 25%)	I	E		
	shivering (> 25%)	I	E		
	weight gain (32%)[9]		E		
Dermatology/skin	cheilitis (24-65%)[2]		E		
	mucosal and skin dryness (24-65%)[2]		E		
	photosensitivity (rare)	I	E		
	pruritus/rash (24-65%)[2]		E		
Gastrointestinal	*emetogenic potential:* rare[17]				
	gastritis (rare)[2]		E		
	nausea/vomiting (51%)[9]	I	E		
Hemorrhage	dermal bleeding (> 25%)		E		
Hepatic	elevated bilirubin (16%)[9]		E		
	elevated hepatic enzymes (> 25%)		E		
Lymphatics	cervical/tonsillar lymphadenopathy (10%)[9]		E		
Metabolic/laboratory	hypercalcemia (rare)[2,18]		E		
	hypercholesterolemia (> 25%)		E		
	hyperhistaminemia (rare)		E		
	hyperlipidemia (rare)[2]		E		
	hypertriglyceridemia (> 25%)		E		
Ocular/visual	visual disturbance, photophobia, conjunctivitis (rare)		E		
Pain	abdominal pain (> 25%)		E		
	arthralgia (20-30%)[2]		E		
	back pain (> 25%)		E		
	bone pain (20-30%)[2]		E		
	chest pain (> 25%)		E		
	headache (29-90%)[2]	I	E		
Pulmonary	coughing (> 25%)		E		
	dyspnea (> 25%)		E		
	nasal congestion (24-65%)[2]		E		
Renal/genitourinary	increased serum creatinine (20-56%)[2]		E		
Sexual/reproductive function	penile or scrotal ulceration (rare)[2,19]		E		
Síndromes	pseudotumor cerebro (rare)[20,21]	I	E		
	retinoic acid syndrome (25%)[2,5]	I	E		
	Sweet's syndrome (rare)[22,23]		E	D	

Adapted from reference “Hoffmann La Roche Ltd. Vesanoid product monograph. Mississauga, Ontario; 7 April 1999”.

Headache occurring several hours after tretinoin ingestion is the most common side effect. It differs from that associated with pseudotumor cerebri in that it is often transient, mild in intensity and well controlled with mild analgesics. Patients usually develop a tolerance with continued tretinoin therapy.

Basophilia/Hyperhistaminemia: Basophilia-associated hyperhistaminemia has been rarely reported. The severity of symptoms depends on the level of plasma histamine. Severe symptoms include tachycardia, shock due to vasodilatation, and gastric and duodenal ulceration. Prophylactic H2- or H1-antagonist has been used to prevent symptoms mediated via H2- and H1-receptors.

Pseudotumor cerebri: Also known as benign or idiopathic intracranial hypertension. It is characterized by signs and symptoms of intracranial hypertension without evidence of infective or space occupying lesions. Symptoms include severe headache which may be aggravated by analgesic or narcotic overuse, nausea and vomiting, papilledema, retinal hemorrhages, visual changes (eg, intermittent visual loss), ophthalmoplegia. The onset of symptoms is about 3-17 days of tretinoin therapy. Pseudotumor cerebri is more common in children than in adults and may be due to their increased sensitivity to the CNS effects of tretinoin. The cause and appropriate management of pseudotumor cerebri have not been established. Narcotic analgesics (eg, codeine, morphine) or temporary discontinuation of tretinoin in non-responding cases may help reduce severe headache, nausea and vomiting. Diuretics (acetazolamide, furosemide) or lumbar puncture may reduce CSF pressure to maintain a final pressure not greater than 15 mm of water.

Retinoic acid syndrome is characterized by some or all of the following symptoms: fever, dyspnea, hypotension, bone pain, respiratory distress, pulmonary infiltrates, hyperleukocytosis, pleural or pericardial effusion, weight gain, lower extremity edema, congestive heart failure, renal failure and multi-organ failure. The earliest manifestations of the syndrome are dyspnea, rales, fever and/or unexplained weight gain. Although the syndrome may occur without concomitant hyperleukocytosis, the risk may be increased if rapidly evolving hyperleukocytosis occurs during tretinoin therapy. The onset of symptoms is about 7-12 days of tretinoin therapy. Potential causes of the syndrome include release of vasoactive cytokines, increased adhesion molecules on myeloid cell surfaces, and acquisition of migratory properties by leukemic cells. Due to the severity and poor prognosis of the syndrome once the full-blown signs have been developed, prophylaxis or early treatment are mandatory:

- For patients with WBC > 5x 10^9 /L at diagnosis of APL or any time during tretinoin therapy, use combination of tretinoin and anthracycline-based chemotherapy.

- For patients with WBC < 5 x 10^9 /L on day 0 of tretinoin therapy and if WBC becomes ≥ 5 x 10^9 /L on day 1-6, ≥ 10 x 10^9 /L on day 7-10, or ≥ 15 x 10^9/L on day 11-28 of tretinoin therapy, add full-dose anthracycline-based chemotherapy to tretinoin therapy.

- For patients with early signs of the syndrome any time during tretinoin therapy, start dexamethasone IV 10 mg every 12 hours for at least 3 days until symptom resolution.

Sweet's syndrome is a hyperinflammatory reaction of neutrophil infiltration of the skin and internal organs. Symptoms include fever, painful erythematous cutaneous plaques involving the extremities and the trunk, and prominent musculoskeletal involvement (eg, myositis, fasciitis). The onset of symptoms is about 7-34 days of tretinoin therapy. The cause of the syndrome is unknown and symptoms generally resolve within 48 hours of corticosteroid therapy.

12.1.9. References

http://www.bccancer.bc.ca/HPI/DrugDatabase/DrugIndexPro/Tretinoin.htm

12.2. Idarubicin

12.2.1. Other Names

Imi 30, NSC-256439.

12.2.2. Classification

Anthracycline antibiotic.

12.2.3. Mode of Action

Idarubicin is an anthracycline analogue of daunorubicin. It is 5 to 6 times more potent and less cardiotoxic than daunorubicin. The mechanism of action of anthracyclines is poorly understood. Cytotoxicity is generally attributed to intercalation of the drug into DNA and/or inhibition of DNA topoisomerase II activity resulting in double and single strand DNA breaks.

12.2.4. Storage and Stability

The reconstituted solution is stable 24 hours at room temperature and 48 hours refrigerated (2-8°C), protected from direct light. However, Trissel's Handbook on Injectable Drugs, 7th Edition, states that the reconstituted solution is physically and chemically stable for 72 hours at room temperature and at least 7 days refrigerated. Like doxorubicin, idarubicin should not be stored in contact with aluminum but may be safely injected through an aluminum-hubbed needle.

12.2.5. Preparation

5 mg, 10 mg vial; contains lactose; store at room temperature (15-30ºC), protect from light. Reconstitute powder with SWI or NS to a final concentration of 1 mg/mL. Do not use bacteriostatic diluents; early experience with doxorubicin suggested that the use of diluents containing benzyl alcohol resulted in hypersensitivity reactions. Vials are under negative pressure.

12.2.6. Administration

Injected into a recently established patent IV site through the side arm of a running IV over 2-5 minutes. Via small (21 or 23) gauge needle into tubing of running IV. Push slowly, so that drip of IV solution does not stop or reverse. Check for blood return before administration and after every 2-3 mL of drug. If no blood return, stop the injection and assess the IV site. Flush with 20 mL NS or D5W after administration to clear any remaining drug from tubing. In children: dilute in 15-20 mL and infuse over 15-30 minutes.

12.2.7. Incompatibilities

Compatible in saline, dextrose, dextrose-saline combinations and lactated Ringer's injection for at least 72 hours at room temperature and protected from light. Dilute solutions (10 mg/L) are light sensitive, undergoing some degradation when exposed to light for periods greater than 6 hours; however, the manufacturer does not recommend special precautions to protect freshly prepared solutions for administration.

Some mixtures with amikacin, cimetidine, cyclophosphamide, cytarabine, diphenhydramine, droperidol, erythromycin, magnesium sulfate, mannitol, metoclopramide, potassium chloride, ranitidine and TPN solution are reported to be compatible during simulated Y-site injection.

It is recommended that idarubicin not be mixed with other drugs. Incompatible with acylcovir, ampicillin, sulbactam, cefazolin, ceftazidime, clindamycin, dexamethasone, etoposide, furosemide, gentamicin, heparin, hydrocortisone, imipenem-cilastin, lorazepam, meperidine, methotrexate, mezlocillin, sodium bicarbonate, vancomycin and vincristine during simulated Y-site injection. Idarubicin is not stable in alkaline solutions.

12.2.8. Availability

Commercially available in 5 and 10 mg glass vials of red colored lyophilized drug.

12.2.9. Side Effects

- Hematologic: Myelosuppression (leukopenia with a nadir between 1-2 weeks)
- Dermatologic: Rash; alopecia; chemical thrombophlebitis or local necrosis if extravasation occurs.
- Gastrointestinal: Nausea, vomiting, commonly occurring one hour after a dose and lasting for several hours; diarrhea, stomatitis.
- Cardiovascular: Arrhythmias, usually transient; congestive cardiomyopathy; maximum total (lifetime) dose of 500-600 mg/m² is recommended because of cumulative cardiotoxicity.
- Renal: Red urine; not hematuria.6. Other: Fever; transient elevations in serum bilirubin, AST, alkaline phosphatase.

12.2.10. Nursing/Patient Implications

- Vesicant - avoid extravasation. Refer to extravasation protocol if inadvertent infiltration occurs.
- Monitor CBC, platelet counts.
- Advise patient of red coloration of urine.
- Administer antiemetics as needed.

12.2.11. References

http://www.bccancer.bc.ca/HPI/DrugDatabase/DrugIndexPro/Idarubicin.htm

12.3. Mitoxantrone

12.3.1. Other Names

DHAD, Dihydroxyanthracenedione dihydrochloride, Mitozantrone, MX, MXR

12.3.2. Classification

Antitumor antibiotic, an anthracenedione structurally similar to doxorubicin.

12.3.3. Mode of Action

The exact mechanism of action is unknown but includes intercalation with DNA to cause inter/intrastrand cross-linking. It also causes DNA strand breaks through binding with the phosphate backbone of DNA. Mitoxantrone is cell cycle phase-nonspecific.

12.3.4. Storage and Stability

Intact vials are stored at room temperature and protected from direct sunlight. Refrigeration may result in a precipitate which redissolves after warming to room temperature. Do not freeze. The manufacturer recommends that unused portions of a vial be discarded.

12.3.5. Preparation

Each 20 mg vial is reconstituted with 4 ml of sterile water to give a final concentration of 5 mg/ml. The desired dose is drawn into a syringe containing 10-15 ml of normal saline. Protect from sunlight.

12.3.6. Administration

Injected into a recently established patent IV site through the side arm of a running IV over 2-5 minutes.

12.3.7. Incompatibilities

It is recommended that mitoxantrone not be mixed with other drugs. Physically incompatible with heparin (precipitate formation). Compatible with ondansetron. Some mixtures with hydrocortisone in NS are reported to be compatible for 24 hours.

12.3.8. Availability

Commercially available in 20 mg glass vi als of dark blue solution.

12.3.9. Side Effects

- Hematologic: Myelosuppression (leukopenia with a nadir between 1-2 weeks)

- Dermatologic: Rash; alopecia; chemical thrombophlebitis or local necrosis if extravasation occurs.
- Gastrointestinal: Mild nausea and vomiting; diarrhea, stomatitis.
- Cardiovascular: Transient arrythmias and congestive heart failure (cardiomyopathy).
- Renal: blue-green urine (for 1-2 days).
- Teratogeny: Fetal damage if pregnancy occurs while receiving this drug.
- Other: Fever; transient elevations in serum bilirubin, AST, alkaline phosphatase. Rare hypersensitivity type I (anaphylactoid).

12.3.10. Nursing/Patient Implications

- Vesicant - avoid extravasation. Refer to extravasation protocol if inadvertent infiltration occurs.
- Monitor CBC, platelet counts.
- Advise patient of blue-green coloration of urine (1-2 days).
- Administer antiemetics as needed.

12.3.11. References

Riggs CE. Antitumor antibiotics and related compounds. In: Perry MC, ed. The chemotherapy source book. Baltimore: Williams & Wilkins; 1992:318-58.

12.4. Cytarabine

12.4.1. Other Names

Cytosar-U, Ara-C, Arabinosyl, cytosine arabinoside.

12.4.2. Classification

Antimetabolite.

12.4.3. Mode of Action

Converted to cytarabine triphosphate (Ara-CTP), a competitive inhibitor of DNA polymerase. The drug is also incorporated into cellular DNA and RNA. It is active against cells in S-phase and is considered to be phase specific.

12.4.4. Storage and Stability

The dry powder is stored at room temperature. After reconstitution, cytarabine is stable for 7 days at room temperature and 15 days refrigerated. Solutions with a slight haze should be discarded.

12.4.5. Preparation

For IV use, reconstitute the 100 mg vial with 5 ml bacteriostatic water for injection to achieve a concentration of 20 mg/ml. Add 10 ml of bacteriostatic water to the 500 mg vial to achieve a final concentration of 50 mg/ml. Add 10 and 20 ml of bacteriostatic water to the 1 and 2 gm vials respectively to achieve a final concentration of 100 mg/ml. For subcutaneous use, reconstitute the powder with sterile water or saline to a concentration of 50-100 mg/ml. For IT use, mix with lactated Ringer's solution or normal saline without preservatives.

12.4.6. Administration

IV push, IV continuous infusion, subcutaneous, or IT. Cytarabine is not absorbed when given orally.

12.4.7. Incompatibilities

Possible interaction with fluorouracil.

12.4.8. Compatibilities

Cytarabine (0.25 mg/ml), daunorubicin (0.03 mg/ml) and etoposide (0.4 mg/ml) are stable in D5/0.45% NaCl for 72 hours at room temperature. Cytarabine is also compatible with sodium chloride, potassium chloride, calcium, and magnesium sulfate.

12.4.9. Availability

Commercially available in 100 mg, 500 mg, 1 gm, and 2 gm vials.

12.4.10. Side Effects

- Hematologic: Leukopenia, thrombocytopenia, anemia, and phlebitis. Nadir occurs in 5-7 days with recovery in 2-3 weeks.
- Dermatologic: Rash, alopecia.
- Gastrointestinal: Nausea, vomiting, diarrhea, dysphagia, mucositis, anorexia.
- Hepatic: Transient increase in liver enzymes.
- Renal: Urinary retention.
- Other: Flu-like syndrome, fever. Profound hyperuricemia may occur in leukemia patients with high white blood counts.
- After intrathecal administration, the most common side effects are nausea, vomiting, fever, and headache, usually mild and self-limiting. Meningism, paresthesia, paraplegia, seizures, blindness, necrotizing encephalopathy have occurred.

12.4.11. Nursing/Patient Implications

- Monitor CBC, platelet counts.
- Patient education related to prolonged myelosuppression.
- Monitor for nausea, vomiting, diarrhea, stomatitis and treat symptomatically.
- Patient/family may need to be taught subcutaneous injection technique.

12.4.12. References

Cheson BD, Jansperse DM, Simon R, et al. A critical appraisal of low-dose cytosine arabinoside in patients with acute non-lymphocytic leukemia and myelodysplastic syndromes. J Clin Oncol 1986; 4:857-864.

12.5. 6-Mercaptopurine

12.5.1. Other Names

6-MP, Purinethol.

12.5.2. Classification

Antimetabolite.

12.5.3. Mode of Action

Mercaptopurine has been in clinical use for over 30 years. It is a 6-thiopurine analogue of the naturally occurring purine bases hypoxanthine and guanine. Intracellular activation results in de novo inhibition of purine synthesis and incorporation into DNA. Mercaptopurine is cross-resistant with 6-thioguanine. Cytotoxicity is cell cycle phase-specific (S-phase).

12.5.4. Storage and Stability

Store at room temperature in tight container.

12.5.5. Preparation

An oral suspension may be extemporaneously prepared at a concentration of 50 mg/ml for oral administration in pediatric patients. Combine crushed tablets with a suspending agent (Cologel) ata a third of the final volume and add a 2:1 mixture of simple syrup and cherry syrup to make up to full volume. This suspension is stable for 14 days when stored at room temperature in a glass amber bottle.

12.5.6. Administration

Oral. Round daily dose to nearest 25 mg (half tablet). Adjust daily doses so that the correct total dose is given each week of therapy. Note that absorption of 6-MP from the GI tract is variable and incomplete with a bioavailability of about 50%.

12.5.7. Incompatibilities

Interaction with allopurinol. Do NOT give Allopurinol with mercaptopurine. Allopurinol, a xanthine oxidase inhibitor, will enhance the toxicity of 6-MP by inhibiting the oxidative metabolism of 6-MP. If 6-MP is given with allopurinol the dose should be reduced by 25% to 33% initially with subsequent dosage based on patient response and toxicity.

12.5.8. Availability

Commercially available as scored 50 mg tablet.

12.5.9. Side Effects

- Hematologic: Leukopenia, thrombocytopenia and anemia (myelosupression).
- Gastrointestinal: Nausea, vomiting, diarrhea, dysphagia, mucositis, anorexia.
- Hepatic: Transient increase in liver enzymes.
- Other: Rash and fever.

12.5.10. References

http://www.bccancer.bc.ca/HPI/DrugDatabase/DrugIndexPro/Mercaptopurine.htm

12.6. Methotrexate

12.6.1. Other Names

Amethopterin, MTX.

12.6.2. Classification

Antimetabolite.

12.6.3. Mode of Action

Methotrexate and its active metabolites compete for the folate binding site of the enzyme dihydrofolate reductase. Folic acid must be reduced to tetrahydrofolic acid by this enzyme for DNA synthesis and cellular replication to occur. Competitive inhibition of the enzyme leads to blockage of tetrahydrofolate synthesis, depletion of nucleotide precursors, and inhibition of DNA, RNA and protein synthesis. Methotrexate is cell cycle phase-specific (S phase).

12.6.4. Storage and Stability

Protect from light; use well-closed containers at 15-300 C.

12.6.5. Preparation

20 mg powder, 2.5 mg/mL solution (preservative-free), 10 mg/mL solution (preservative-free), and 25 mg/mL solution (preservative-free or preserved with benzyl alcohol). Store at room temperature, protected from light. Reconstitute 20 mg powder with 2-10 mL NS, D5W or SWI to desired concentration. Stable at least 1 week at room temperature protected from light. However, the manufacturers recommend

reconstitution immediately before use and that unused portions of vials reconstituted with preservative-free diluents be discarded. For oral prescription, tablets of 2.5 mg are available. For oral prescription tablets of 2.5 mg are available.

12.6.6. Administration

Intramuscular or orally.

12.6.7. Incompatibilities

Aminoglycosides may cause decreased absorption of MTX, and increased renal toxicity. Folic acid decrease response to MTX. The use of NSAIDs may increase MTX levels. Probenecid, salicylates, sulfonamides may increase therapeutic and toxic effect of MTX. Procarbazine can cause increased nephrotoxicity. Teophylline may increase plasma levels. Alcohol may result in increased hapatotoxicity. Thiazides may cause granulocytopenia. Food will delay absorption, and decreases MTX peak.

12.6.8. Availability

Commercially available in 25 mg vials.

12.6.9. Side Effects

- Hematologic: Leukopenia, thrombocytopenia, and anemia.
- Dermatologic: Pruritis, urticaria, photosensitivity.
- Gastrointestinal: Nausea, vomiting, diarrhea, dysphagia, mucositis, anorexia.
- Hepatic: Transient increase in liver enzymes. Hepatic fibrosis and cirrhosis with long term therapy
- Pulmonary: Pneumonitis. Pulmonary fibrosis that is not dose-dependent.
- Renal: Renal failure, cystitis, dysuria, hematuria.
- CNS: drowsiness, blurred vision, tinnitus, malaise, seizures.
- Other: Diabetes.

12.6.10. References

http://www.bccancer.bc.ca/HPI/DrugDatabase/DrugIndexPro/Methotrexate.htm

13. STATISTICAL CONSIDERATIONS

This study differs from the usual non-randomized phase II study, in that its primary objectives are to estimate the CR rate, duration of remission, event-free, disease free and overall survival, and side effects of the induction, consolidation and maintenance treatment that are not regarded as experimental, but as a standard for APL.

The study will serve to investigate whether with a slight modification of the regimen used in the previous PETHEMA study,[12] the results obtained in that study can be reproduced and whether there is some indication of some improvements.

The study is a one-stage design with no early stopping rule. The planned duration of the study is 3 years and with an expected yearly accrual of 100 patients the target number of patients in this study is 300.The PETHEMA group reported[12] the CR rate of 90% with the induction regimen of oral ATRA 45 mg/m^2/d until CR or for a maximum of 90 days and idarubicin 12 mg/m^2/d on days 2,4,6, and 8 and a probability of relapse after CR of about 30% at 3 years in the high risk group.

About 25% of the registered patients are high risk. With 300 patients entered and a CR rate of about 90% the standard error of the CR rate estimate in this study will be 1.7%. It is expected that about 65 high risk patients will reach a CR. If the relapse rate in this subgroup will be between 20 and 30% the standard error in this estimate will be between 5% and 6%.

Disease-free, event-free, and overall survival, as well as duration of remission will be estimated using the Kaplan-Meier method. The Cox regression model will be employed for multivariate analysis of prognostic factors. Cumulative incidence curve for relapse will be constructed reflecting time to relapse and time to death without relapse as competing risks (Gray, 1988). The outcomes will be compared with the results obtained in the previous studies with multivariate logistic and Cox regression depending on the endpoint, eg. hemorrhage, toxicity and CR rate with logistic regression and overall and disease free survival with Cox regression.

14. ETHICS

14.1. Independent ethics committee or Institutional review board

The study protocol and any amendment that is not solely of an administrative nature will be approved by an Independent Ethics Committee or Institutional Review Board.

14.2. Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (South Africa Amendment 1996) and the ICH-GCP Guidelines of 17 January 1997.

14.3. Patient information and consent

Informed consent of patients is required before entering in the study. The procedure and the risks and the opinions for post-induction therapy in APL will be explained to the patient.

15. TRIAL INSURANCE

HOVON will ensure that insurance is in place for all participating sites.

HOVON will provide risk insurance to cover all patients from participating sites in the Netherlands according to Dutch law (WMO).
In case of an intergroup study, risk insurance of patients from centers participating within another cooperative group will be provided by that group, according to all applicable laws and regulations.
Individual participating centers from outside the Netherlands have to arrange risk insurance of their own patients according to all applicable laws and regulations.

16. REFERENCES

1. Tallman MS, Nabhan Ch, Feusner JH, Rowe JM. Acute promyelocytic leukemia: evolving therapeutic strategies. Blood 2002; 99:759-67.

2. Ohno R, Asou N, Ohnishi K. Treatment of acute promyelocytic leukemia: strategy toward further increase of cure rate. Leukemia. 2003;17:1454-63.

3. Sanz MA, Martín G, Lo Coco F. Choice of chemotherapy in induction, consolidation and maintenance in acute promyelocytic leukemia. Baillieres Best Pract Res Clin Haematol 2003; 16: 433-51.

4. Sanz MA, Martín G, Rayón C, et al. A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RAR? -positive acute promyelocytic leukemia. Blood. 1999;94:3015-3021.

5. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans retinoic acid in acute promyelocytic leukemia. N Engl J Med. 1997;337:1021-1028.

6. Mandelli F, Diverio D, Avvisati G, et al. Molecular remission in PML/RAR? -positive acute promyelocytic leukemia by combined all-trans retinoic acid and idarubicin (AIDA) therapy. Blood. 1997;90:1014-1021.

7. Asou N, Adachi K, Tamura J, et al. Analysis of prognostic factors in newly diagnosed acute promyelocytic leukemia treated with all-trans retinoic acid and chemotherapy. J Clin Oncol. 1998;16:78-85.

8. Burnett AK, Grimwade D, Solomon E, Wheatley K, Goldstone AH, on behalf of the MRC Adult Leukemia Working Party: Presenting white blood cell count and kinetics of molecular remission predict prognosis in acute promyelocytic leukemia treated with all-trans retinoic acid: result of the randomized MRC trial. Blood. 1999;93:4131-4143.

9. Fenaux P, Chastang C, Sanz MA, et al. A randomized comparison of ATRA followed by chemotherapy and ATRA plus chemotherapy, and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. Blood. 1999;94:1192-1200.

10. Lengfelder E, Reichert A, Schoch C, et al. Double induction strategy including high dose cytarabine in combination with all-trans retinoic acid: effects in patients with newly diagnosed acute promyelocytic leukemia. Leukemia 2000;14:1362-70.

11. Sanz MA, Lo Coco F, Martín G, et al. Definition of relapse risk and role of non-anthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. Blood 2000; 96: 1247-1253.

12. Sanz M, Martin G, Gonzalez M, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans-retinoic acid and anthracycline monochemotherapy: a multicenter study by the PETHEMA group. Blood. 2004 ; 103:1237-43.

13. Lo Coco F, Avvisati G, Vignetti M, et al. Front-Line Treatment of Acute Promyelocytic Leukemia with AIDA Induction Followed by Risk-Adapted Consolidation: Results of the AIDA-2000 Trial of the Italian GIMEMA Group. Blood 2004; 104 (suppl 1): 392 (abstract)..

14. Grimwade D, Gorman P, Duprez E, et al. Characterization of cryptic rearrangements and variant translocations in acute promyelocytic leukemia. Blood. 1997;90:4876-4885

15. van Dongen JJM, Macintyre EA, Gabert J, et al. Standardized RT-PCR analysis of fusion gene transcripts from chromosome aberrations in acute leukemia for detection of minimal residual disesase. Leukemia 1999; 13, 1901-1928.

16. Falini B, Flenghi M, Lo Coco F. et al. Immunocytochemical diagnosis of acute promyelocytic leukemia (M3) with the monoclonal antibody PG-M3 (anti-PML). Blood 1997; 90:4046-4063.

17. Gomis F, Sanz J, Sempere A, Plumé G, Senent ML, Pérez ML, Cervera J, Moscardó F, Bolufer P, Barragán E, Martín G, Sanz MA. Immunofluorescent analysis with the anti-PML monoclonal antibody (PG-M3) for the rapid and accurate genetic diagnosis of acute promyelocytic leukemia. Ann Hematol 2004; 83: 687-690.