PETHEMA/PALG

Treatment of Acute Promyelocytic Leukemia

PETHEMA LPA 2017

Remission induction and consolidation with ATRA + arsenic trioxide (ATO) in low/intermediate risk APL patients aged ≥ 70 years old.

Remission with idarubicin with ATRA plus Idarubicin and consolidation with anthracyclines, citarabine and ATRA in high risk APL patients aged < 70 years old.

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SYNOPSIS

<table>
<tr><td>Objectives</td><td>To provide a risk-adapted strategy for patients diagnosed with low and intermediate risk APL treated with a combination of ATO+ATRA and for patients diagnosed with high risk APL treated with chemotherapy based on anthracyclines and ATRA.</td></tr>
<tr><td>Patient population</td><td>Patients with genetic diagnosis of acute promyelocytic leukemia (APL)</td></tr>
<tr><td>Phases and duration of treatment</td><td>
<u>Low and intermediate risk (leucocytes ≤10 x 10^9/L) or age ≥70</u>
Induction: therapy with ATO 0,15 mg/kg/daily administrated every 2 hours intravenous (IV) infusion combined with ATRA 45mg/m^2/daily administrated orally until CR (minimum 28 days) or for a maximum of 60 days.

<u>Consolidation</u> 1-4 (duration 28 weeks)
<table>
<tr><td>ATO</td><td>0,15 mg/kg</td><td>i.v</td><td>Days 1-5 (4 weeks with ATO followed by 4 weeks without ATO, for a total of 4 cycles)</td></tr>
<tr><td>ATRA</td><td>45 mg/m^2</td><td>v.o</td><td>Days 1-14 (2 weeks with ATRA followed by 2 weeks without ATRA till finish ATO, for a total of 7 cycles)</td></tr>
</table>
Doses of ATRA should be reduced to 25 mg/m^2 in patients < 20 years old. Between 67 and 80 kg of weight, it is possible to administer ATO in fixed doses of 10 mg/day (1 vial), while for all other patients exact doses of 0,15 mg/kg/daily is recommended (do not exceed doses of 20 mg/daily).

High risk APL (leucocytes >10 x 10^9/L) and age < 70 years old

Induction with simultaneous ATRA (45 mg/m^2 day until CR, maximum for 60 days) and idarubicin (12 mg/m^2 daily on days 1, 3, 5 and 7; in patients <u>≥</u> 60 years old, the dose from day 7 is suppressed.

Three monthly consolidation courses with ATRA (45 mg/m^2/d, days 1–15), anthracyclines and ara-C with risk-and age-adapted dose.
1. All patients aged between 60 and 68 years: course 1 with ATRA and idarubicin (5 mg/m^2/d, days 1–4); course 2 with ATRA and mitoxantrone (10 mg/m^2/d, days 1–3); course 3 with ATRA and idarubicin (12 mg/m^2/d, day 1)
2. If < 60 years old: course 1 with ATRA, idarubicin (5 mg/m^2/d, days 1–4) and ara-C (1000 mg/m^2/d, days 1–4); course 2 with ATRA and mitoxantrone (10 mg/m^2/d, days 1–5); course 3 with ATRA, idarubicin (12 mg/m^2/d, day 1) and ara-C (500 mg/m^2/d, days 1–4)

For maintenance therapy: two cycles of ATRA+ATO should be administered

Maintenance 1-2 (duration 12 weeks)
<table>
<tr><td>ATO</td><td>0,15 mg/kg</td><td>i.v</td><td>Days 1-5 (4 weeks with ATO followed by 4 weeks without ATO, for a total of 2 cycles)</td></tr>
<tr><td>ATRA</td><td>45 mg/m^2</td><td>v.o</td><td>Days 1-14 (2 weeks with ATRA followed by 2 weeks without ATRA till finish ATO, for a total of 7 cycles)</td></tr>
</table>
</td></tr>
<tr><td>Central nervous system prophylaxis</td><td>Only for patients with documented central nervous system (CNS) bleeding at diagnosis or during induction therapy</td></tr>
</table>

APL 2017 THERAPEUTIC SCHEME

APL PML/RARa (+)
Start ATRA if

*Low / intermediate***
(WBC ≤10 x 10⁹ /L)

Induction (ATO+ATRA)
ATRA 45 mg/m²/d p.o. from +1 to CR
ATO 0,15 mg/kg i.v. from +1 to CR
Prednison 0,5 mg/kg p.o. x 21 days

Consolidation

ATRA 45 mg/m²/d x 14 d (week 1-2 i 5-6)
ATO 0.15 mg/kg/d Monday-Friday (week 1-4)

ATRA 45 mg/m²/d x 14 d (week 1-2 i 5-6)
ATO 0,15 mg/kg/d Monday-Friday (week 1-4)

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ATO 0.15 mg/kg/d Monday-Friday (week 1-4)

ATRA 45 mg/m²/d x 14 d (week 1-2)
ATO 0.15 mg/kg/d Monday-Friday (week 1-4)

*** Also high risk if APL sec or >= 75 r.ż.*

High risk
(WBC >10 x 10⁹ /L)

Induction (AIDA)
IDA 12 mg/m²/d days 1,3,5,7 (≥60 y.o. days 1,3,5)
ATRA 45 mg/m²/d p.o. from +1 to CR
Prednison 0,5 mg/kg p.o. x 21 days

Consolidation

Age ≥ 60 r.ż.

IDA 5 mg/m²/d (days 1,2,3,4)
ATRA 45 mg/m²/d x 15

MTZ 10 mg/m²/d (days 1,2,3)
ATRA 45 mg/m²/d x 15

IDA 12 mg/m²/d (day 1)
ATRA 45 mg/m²/d x 15

Age < 60 r.ż.

IDA 5 mg/m²/d (days 1,2,3,4)
Ara-C 1000 mg/m²/d (days 1,2,3,4)
ATRA 45 mg/m²/d x 15

MTZ 10 mg/m²/d (days 1,2,3,4,5)
ATRA 45 mg/m²/d x 15

IDA 12 mg/m²/d (day 1)
Ara-C 500 mg/m²/d (day 1,2,3,4)
ATRA 45 mg/m²/d x 15

Mantainment

ATRA 45 mg/m²/d x 14 d (week 1-2 i 5-6)
ATO 0,15 mg/kg/d Monday-Friday (week 1-4)

ATRA 45 mg/m²/d x 14 d (week 1-2 i 5-6)
ATO 0,15 mg/kg/d Monday-Friday (week 1-4)

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1. INTRODUCTION

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]

In order to improve the outcome results of the PETHEMA LPA96 protocol (which consists of induction and consolidation with ATRA and anthracyclines in monotherapy followed by maintenance) [2], the new PETHEMA LPA99 protocol, which was designed based on a relapse risk-adapted strategy, was performed in cooperation with the PETHEMA and GIMEMA groups. With this protocol, the rate of relapse was significantly reduced in patients at intermediate and high risk, without an excessive increase in the toxicity of the consolidation courses. However, the cumulative incidence of relapse in high risk patients remained increased (27% at 5 years).[3]

The next step was the design of the PETHEMA LPA 2005 protocol, which was based on the results of the GIMEMA AIDA 2000 protocol, in which high risk patients under the age of 60 received a treatment regimen similar to LPA99, but ara-C was included in cycles 1 and 3 of the consolidation. The LPA 2005 study achieved its objectives, with a significant decrease in hematological toxicity in low and intermediate risk patients, without increasing the relapse rate; and a decrease in the cumulative incidence of relapse in high risk patients.[4] The PETHEMA LPA 2012 protocol refined the previous protocol LPA 2005, reducing the doses of idarubicin and adding ara-c in intermediate-risk patients under the age of 60, and decreasing the cumulative dose of anthracyclines in all patients older than 60 years. The preliminary (unpublished) results of the LPA 2012 protocol, show that there is no global improvement regarding the LPA 2005 protocol.

It can be affirmed that "standard" treatments with the combination of ATRA and chemotherapy result in an overall survival of around 85-90% in those patients eligible for the protocols.[5] However, a substantial part of the patients are not considered eligible for conventional chemotherapy and ATRA protocols, especially in the population older than 60-70 years, for different reasons: 1) not being considered candidates for chemotherapy due to comorbidities or very old age, 2) contraindication for the administration of anthracyclines (especially due to having previously received high doses accumulated by a previous neoplasm or due to poor cardiac function with LVEF% <50%), 3) having a previous neoplasia (secondary LPA), and 4) having a very bad general condition due to a bleeding or infectious complication related to the same APL. Thus, under conditions of "real life", survival in the LPA can be closer to 70-80%.[6] Consequently, there is room for improvement even greater than that which can be expected in the treatment of APL.

Recently, two randomized studies conducted at the same time by the Italian group GIMEMA7 and the British group NCRI,8 have suggested that first-line treatment with the ATO + ATRA combination may even be superior to the "standard" first-line treatment with chemotherapy and ATRA in patients with APL of intermediate and low risk. These two clinical trials explored two different ATO + ATRA regimens, comparing their results with classic chemotherapy and ATRA guidelines, showing a lower relapse rate and an improvement in survival in patients treated with ATO + ATRA (> 90%). It should be noted that in the study of the GIMEMA group, although an improvement in survival was reported in patients with intermediate and low risk, the most important difference between the two treatment branches was observed in the safety profile of the ATO + branch. ATRA, which was substantially less cytotoxic than the branch with chemotherapy. This had an impact on the quality of life and hospital admissions, thus being able to partially justify the increase in direct pharmacological expenditure derived from the use of ATO. The treatment regimen of the ATO + ATRA regimen of the GIMEMA group did not include prolonged maintenance, unlike the regimens with ATRA and chemotherapy, this being a potential advantage for the quality of life and the care costs related to patient management. Although there is still no consensus on the superiority of the ATO + ATRA regimen regarding the best regimens with ATRA and chemotherapy, in December 2016 the EMA (European Medicines Agency) gave its approval for the indication of ATO in the first treatment line of patients with LPA of low and intermediate risk. To date, this drug has only been indicated in the rescue treatment for second line APL.

These new LPA treatment guidelines are based on the excellent results obtained with ATO + ATRA in patients with intermediate and low risk. However, these results must be validated in real life in prospective or retrospective studies conducted in large patient groups. On the other hand, patients with high-risk APL do not yet have the possibility of treatment with ATO + ATRA in the first line, and it is unknown if this combination is equally safe in induction, or if it provides long-term benefits with respect to classic ATRA guidelines and chemotherapy. It should be noted that in 2017 a randomized, pan-European clinical trial (APOLLO) was started in which the ATO + ATRA regimen will be compared with the PETHEMA LPA2005 scheme for patients <65 years of age with high-risk APL. For these reasons, the PETHEMA LPA2017 recommendations for high-risk patients will consist of the combination of ATRA and chemotherapy, according to the previous protocol (LPA2012).

In this protocol, the use of ATO + ATRA is recommended independently of the risk group in the following special situations: 1) patients aged ≥70 years: patients of these ages tolerate chemotherapy with a high associated mortality in a particularly bad way; many times they do not receive a complete therapeutic scheme, so, in them, a regime based on ATO + ATRA may be especially useful; 2) patients with cardiac comorbidity (LVEF <50%) or other

contraindication for receiving anthracyclines. However, a first line with ATO + ATRA can not be recommended in situations in which ATO is contraindicated (as patients with prolongation of the QTc> 500 msg in the electrocardiogram).

Finally, it is proposed to replace prolonged maintenance of 2 years with chemotherapy by two cycles of ATO + ATRA in patients with high-risk APL. This is due to the burden for patients and centers receiving prolonged maintenance with oral chemotherapy and ATRA (whose utility is not clearly demonstrated). However, we consider it prudent to replace 2-year maintenance with two cycles of ATO + ATRA to prevent the high risk of relapse that this subgroup of patients still shows.

The results obtained in this protocol will be compared retrospectively with those reported in patients with LPA of the Epidemiological Registry of LMA PETHEMA, treated with the protocols LPA96 to LPA2012.

2. PATIENTS WHO APPLY THESE RECOMMENDATIONS

2.1. Inclusion criteria

- New diagnosis of APL
- 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,[1] PML-RARα rearrangement detected by RT-PCR or FISH, microspeckled PML protein pattern demonstrated by PG- M3 monoclonal antibody. Obviously, the results of these tests may become available after having initiated the treatment based on a tentative morphological diagnosis.

2.2. Exclusion criteria

- ECOG 4
- Age >90 years
- The patient must not have received any systemic definitive treatment for APL, including cytotoxic chemotherapy or retinoids. Prior therapy with corticosteroids, hydroxyurea or leukapheresis will not exclude the patient.
- APL with variant translocation

- Cardiac insufficiency grade III-IV
- Serum creatinine ≥ 250 µmol/l (≥ 2.5 mg/dL)
- Bilirubin, alkaline phosphatase, or SGOT > 3 times the upper limit of normality (ULN)
- HIV seropositivity
- Presence of an associated active neoplasm.
- Presence of a severe psychiatric disease.
- Positive pregnancy test

2.3. Exclusion criteria for the use of ATO

- Congenital QT prolongation syndrome
- History or presence of significant tachycardia ventricular o auricular
- Resting bradycardia clinically significant (< 50 beats by minute)
- QTc > 500 msec in EKG (calculated by the QTc formula explained in 8.2 section)
- Hypersensitivity to ATO or any of the excipients
- Right branch block with hemiblock left anterior or bifascicular block

CLARIFICATION:

Even if the patients are not eligible, they will be treated according to these guidelines unless there is a contraindication for this purpose according to the investigator criteria.

These protocols reflect the usual practice in medicine

No intervention is applied to patients, either diagnostic or follow-up, that is not the usual clinical practice decided freely by each institution.

3. REGISTRATION REQUIREMENTS

3.1. Inclusion criteria

The patient or patients' legally authorized guardian 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. Patients can be registered in the Epidemiological record or in diagnostic platform of PETHEMA (PLATAFO-LMA) once they have been asked for permission, so that the data of their illness can be used by this Registry (informed consent: Appendices I).

3.2. Confirmation of Genetic Diagnosis

Bone marrow (BM) sample collection before treatment is mandatory. The demonstration of t(15;17) or of its counterpart, the hybrid gene PML/RARα, should be carried out with karyotype, FISH or RT-PCR (see Section 5 for requirements of samples, instructions to send the samples and protocols for the cytogenetic methods, FISH or RT-PCR and PML immunostaining). However, the strategy to establish the genetic diagnosis should take into account advantages and disadvantages of different but complementary methods. For example, although the use of the PML immunostaining method is an interesting option for a quick and safe diagnosis of APL, this technique should not replace RT-PCR, given that the later defines the PML//RARα isoform, necessary to monitor the minimal residual disease in each individual patient.

4. DIAGNOSTIC STUDIES, SHIPMENT AND SAMPLE BANKING

4.1. Laboratory studies as a regular practice of the center

4.1.1. Sample centralization and banking

At diagnosis, the following material should be collected and stored in laboratories that assume the responsibility of genetic diagnosis:

- 3-4 BM smears and 3-4 peripheral blood (PB) smears without staining. 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 BM aspirate vial (1-2 ml) in sodium citrate. One PB vial (5-20 ml) in sodium citrate or EDTA (preferably EDTA). Shipment to NRL is recommended at 4 °C. for extraction of RNA and RT-PCR analysis of PML/RAR. Isolated mononuclear cells in guanidium isotiocyanate (GTC) will be stored for banking at – 20 °C.
- BM aspirate (1-2 ml) will be collected in 6 ml of heparinized RPMI (with FCS and antibiotics) and shipped at room T for karyotypic and FISH studies.

4.1.2. Conventional karyotyping.

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

4.1.3. FISH analysis of PML/RARα

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/RARα is reported in details in ref. 9

4.1.4. RT-PCR analysis of PML/RARα

RT-PCR analysis will be carried out preferably on RNA extracted from BM. The protocol to be adopted for RT-PCR analysis of PML/RARα is the one designed by the Biomed-1 Concerted Action.[10]

4.1.5. 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. 11 and 12.

5. PATIENT REGISTRATION AND DATA SUBMISSION

To avoid selection bias, it is recommended to communicate all patients diagnosed with APL, whether "eligible" or not, in the PETHEMA LMA epidemiological registry.

5.1. Patient registration in the PETHEMA Diagnostic Platform (PLATAFO-LMA)

See protocol PLATAFO-LMA

5.2. Communication of patients in PETHEMA epidemiological registry

See PETHEMA Epidemiological Record

5.3. Information required for registration

See PETHEMA Epidemiological Record

6. CRITERIA FOR RECEIVING ATO + ATRA or ATRA + CHEMOTHERAPY

6.1. Patients in which the ATO + ATRA scheme will be applied, if at least one criterion is met:

1) Low and intermediate risk (leukocytes ≤ 10 x 10^9 / L).

2) Age ≥70 years, regardless of the risk group.

3) Cardiac comorbidity (LVEF <50%) or other clear contraindication to receive anthracyclines, regardless of the risk group.

6.2. Patients in which the ATRA + QT scheme will be applied, if at least one criterion is met:

1) High-risk LPA (leukocytes> 10 x 10^9 / L) and age <70 years.

2) Contraindication of the ATO (especially in those cases with prolongation of the QTc> 500 msg in the electrocardiogram), regardless of the risk group. If age <60 years and leukocytes > 10 x 10^9 / L, follow the ATRA + QT guideline for high risk, if age <60 years and leukocytes ≤ 10 x 10 9 / L follow intermediate risk arm of LPA2012, if age > 60 years follow the guideline of age ≥60 years.

7. ATRA + SCHEME CHEMOTHERAPY

7.1. Induction Treatment

See instructions in section 6.

7.1.1. Induction chemotherapy (AIDA)

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

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

– The treatment with ATRA will continue until CR is achieved (advisable for a minimum of 28 days) or for a maximum of 60 days in case of persistence of atypical promyelocytes in the bone marrow.

Idarubicin, 12 mg / m² on days 1, 3, 5 and 7 of treatment by intravenous infusion (5-20 min).

– In patients aged between 60 and 69 years, only 3 doses of idarubicin will be administered (days 1, 3 and 5)

– If for any reason idarubicin can not be started on day 1, cytoreduction with hydroxyurea (1.5 to 3 grams / day) will be started until idarubicin can be started.

7.1.2. Support measures in induction

Prednisone: 0.5 mg / kg / day for the first 14 days from the start of ATRA in all patients.

Antibacterial and antifungal prophylaxis: it is recommended to administer ciprofloxacin 500 mg / 12h and fluconazole 100 mg / 24h VO from the start of chemotherapy to recovery of neutrophil count > 0.5-1 x 10^9 / L.

Hydration: taking into account the high risk of liquid retention in these patients (frequent blood product transfusions, differentiation syndrome) and the low rate of chemotherapy-related nephrotoxicity, a not excessive hydration is recommended (maximum 1.5 l / m^2 / day).

Transfusion: of platelet concentrates to maintain counts above 30x10^9 / L during the first 10 days and packed red blood cells (PRC) to maintain hemoglobin levels above 9 g / dL (5.5 µmol / l). In patients with a very high risk of fatal bleeding (hyperleukocytosis > 10 x 10^9 / L, or abnormal creatinine, or consumption coagulopathy, defined as the presence of hypofibrinogenemia or prolonged APTT, thrombin time, or prothrombin time, together with elevation of D-dimers or fibrinogen degradation products) platelets transfusion should be given for achieving more than 50 x 10^9 / L.

In all patients, the hemostatic parameters should be corrected with fibrinogen or cryoprecipitate (to maintain serum fibrinogen higher than 150 mg/dL) and/or plasma (to maintain a Quick Index above 60% or INR under 1.3). In patients with severe differentiation syndrome and/or liquid overload, prothrombin complex concentrate can be administered instead. Nevertheless, signs and symptoms of thrombosis should be guarded. The use of recombinant FVII should be restricted to patients with refractory coagulopathy (not corrected in spite of the standard support measures previously described) who also present potentially lethal bleedings.

Anticoagulant measures: the use of heparin and antifibrinolytics are not recommended as prophylaxis. In case of severe venous or arterial thrombosis the patients will require heparin and/or fibrinolytics, but the elevated bleeding risk should be taken into account if they present coagulopathy and/or platelet counts under 50 x 109/L. If a thrombotic /ischemic cerebrovascular accident takes place, in which the bleeding transformation would be life threatening, anticoagulation should be postponed until the resolution of the coagulopathy.

Growth factors: the use of granulocytic colony growth factors is not recommended during induction (they will only be allowed in case of severe neutropenia and life threatening infection at the same time).

7.1.3. Modifications of Idarubicin Dose during Induction Treatment

In case of hepatotoxicity with a bilirubin greater than 80 µmol/l (3.0 mg/dl), 75 % of the original dosage should be given.

7.1.4. Modification of ATRA Dose during Induction Treatment

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

Differentiation syndrome (DS):

It is mandatory to resort to prophylaxis with prednisone, in a dose of 0.5 mg / kg / day VO during the first three weeks of induction. During treatment with holo-transretinoic acid (ATRA) and / or ATO, differentiation syndrome (SD) can develop rapidly. The diagnosis must be confirmed clinically.

This syndrome should be suspected in the presence of any of these signs and symptoms (without definitive alternative cause to explain them): respiratory distress, hypoxemia, pulmonary infiltrates, pleural or pericardial effusion, hypotension, peripheral edema or weight gain, with or without presence of hyperleukocytosis. In this case, the following measures should be adopted immediately:

- **Dexamethasone**, 10 mg/12 h IV a minimum of 3 days and until the signs and symptoms of the differentiation syndrome disappear.
- In some cases the administration of furosemide is necessary
- Temporary withdrawal of ATRA treatment in those cases of severe differentiation syndrome.13 Serious DS is considered when at least 3 of the following criteria are presented:

1-Dyspnea / hypoxemia

2-Unexplained fever

3-Interstitial lung infiltrates (or intersitioalvelares)

4-Pleural or pericardial effusion

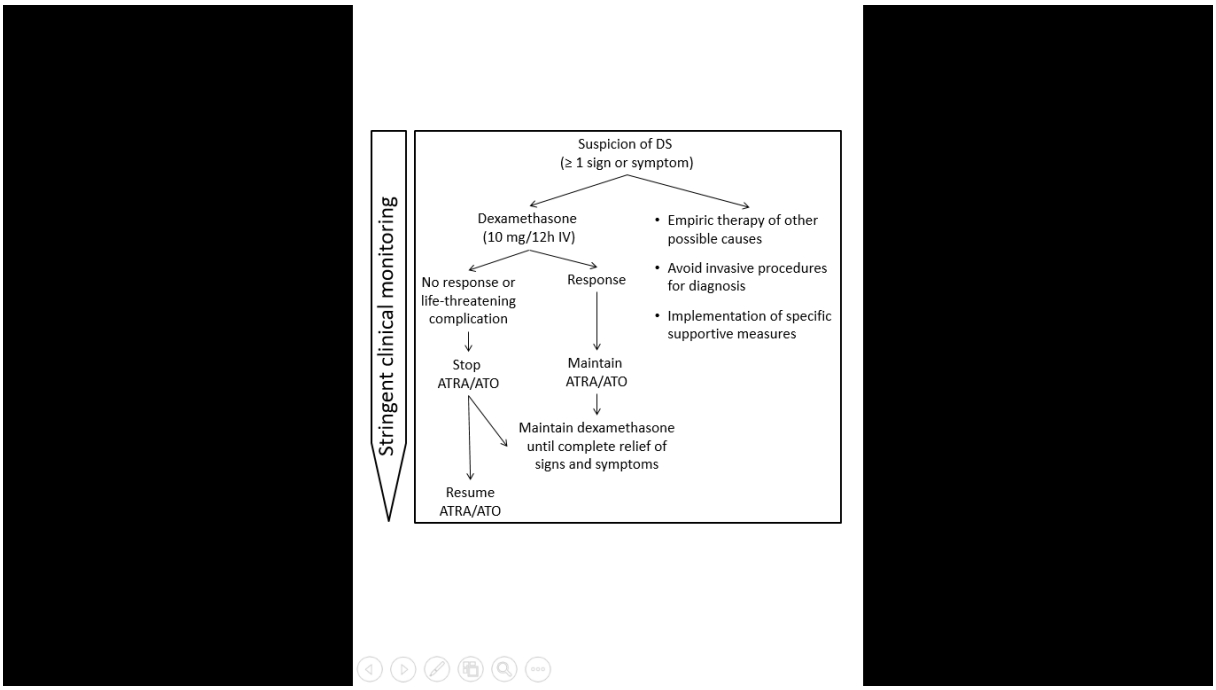
5-Arterial hypotension

6-Acute kidney failure

7-Weight gain > 5kg (or > 10% basal weight)

Closely monitoring of vital signs and early transfer of APL patients to the ICU should be considered in case of diagnosis of severe differentiation syndrome. As soon as the patient's clinical situation improves and the symptoms have disappeared, treatment with ATRA should be resumed. In the absence of worsening of the previous toxicity, treatment with ATRA should continue with the full dose.

Figure 1: Algorithm of DS management (adapted from Sanz et al). [14]



Pseudotumor cerebri syndrome: Its incidence can be up to 13% in pediatric patients, and up to 5% in adults aged <25 years. It manifests with headache, nausea, vomiting and blurred vision (signs of endocranial hypertension), in the absence of space-occupying lesion. It is often necessary to temporarily stop treatment with ATRA and administer opioid analgesics and osmotic diuretics (acetazolamide). As soon as the patient's symptoms and clinical situation improve, treatment with ATRA should be resumed. If symptoms persist it may be necessary to reduce the ATRA dose by 50%.

Hepatotoxicity: An increase in serum bilirubin, GOT / GPT or alkaline phosphatase 5 times normal values will force a temporary suspension of ATRA.

As soon as the patient's symptoms and clinical condition improve, treatment with ATRA can start again immediately.

7.2. Consolidation Treatment

Once hematological recovery is achieved (PMN > $1.5x10^9$/l and platelets > $100x10^9$/l), patients who achieve CR undergo three successive cycles of consolidation chemotherapy in a monthly schedule if the hematological recovery between cycles allows it.

7.2.1. High risk patients aged between 60 and 69 years

High-risk patients are those with a white blood cell count at diagnosis > 10 x 10^9/L, regardless of the platelet count.

Patients in other special situations should receive this scheme (see section 6.2).

Under appropriate circumstances, the administration of consolidation chemotherapy is recommended to be performed in out-patient clinic. Admission to hospital is necessary only if the clinical situation requires it.

Antibacterial and antifungal prophylaxis: it is recommended to administer ciprofloxacin 500 mg / 12h and fluconazole 100 mg / 24h VO from the start of the ATO to the recovery of neutrophil count > 0.5-1 x 10^9 / L.

7.2.2.1. First consolidation cycle

Idarubicin , 5 mg / m² / day by intravenous infusion (5-20 min) on days 1, 2, 3 and 4.

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

7.2.1.2. Second consolidation cycle

Mitoxantrone , 10 mg / m² / day by intravenous infusion (5-20 min) on days 1, 2, 3.

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

7.2.1.3. Third consolidation cycle

Idarubicin , 12 mg / m² / day by intravenous infusion (5-20 min) only on day 1.

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

7.2.1. High risk patients aged less than 60 years.

High-risk patients are those with a white blood cell count at diagnosis > 10 x 10^9/L, regardless of the platelet count.

Patients in other special situations should receive this scheme (see section 6.2).

Under appropriate circumstances, the administration of consolidation chemotherapy is recommended to be performed in out-patient clinic. Admission to hospital is necessary only if the clinical situation requires it.

Antibacterial and antifungal prophylaxis: it is recommended to administer ciprofloxacin 500 mg / 12h and fluconazole 100 mg / 24h VO from the start of the ATO to the recovery of neutrophil count > 0.5-1 x 10^9 / L.

7.2.2.1. First consolidation cycle

Idarubicin, 5 mg / m² / day by intravenous infusion (5-20 min) on days 1, 2, 3 and 4.

Ara-C, 1000 mg / m² / day by continuous intravenous infusion (6 hours) on days 1, 2, 3 and 4.

ATRA, 45 mg / m² / day fractionated into 2 doses on days 1 to 15. In those under 20 years of age, the dose of ATRA will be reduced to 25 mg / m² / day divided into 2 doses.

7.2.2.2. Second consolidation cycle

Mitoxantrone , 10 mg / m² / day by intravenous infusion (5-20 min) on days 1, 2, 3, 4 and 5.

ATRA , 45 mg / m² / day fractionated into 2 doses on days 1 to 15. In those under 20 years of age, the dose of ATRA will be reduced to 25 mg / m² / day fractionated into 2 doses.

7.2.2.3. Third consolidation cycle

Idarubicin , 12 mg / m² / day by intravenous infusion (5-20 min) on day 1.

Ara-C , 500 mg / m² / day by continuous intravenous infusion (6 hours) on days 1, 2, 3 and 4.

ATRA , 45 mg / m² / day fractionated into 2 doses on days 1 to 15. In those under 20 years of age, the dose of ATRA will be reduced to 25 mg / m² / day fractionated into 2 doses.

7.2.3. Dose modifications during consolidation treatment.

7.2.3.1. Modifications of the ATRA dose.

ATRA will be temporarily withdrawn if the following complications occur:

Pseudotumor cerebri syndrome: see section 7.1.4.

Hepatotoxicity: see section 7.1.4.

The appearance of ATRA syndrome is not expected once complete remission is achieved.

7.2.3.2. Modifications of doses of Idarubicin and Mitoxantrone.

In case of hepatotoxicity with a bilirubin > 3 mg / dl, 75% of the original dosage of Idarubicin should be given.

An adequate left ventricular function is required. Patients with left ventricular dysfunction will be discussed individually; if it is possible, proceed directly to maintenance therapy without anthracyclines consolidation.

7.2.4. Prophylaxis of CNS relapse with intrathecal chemotherapy in patients with CNS bleeding at APL diagnosis or during induction therapy.

This should only be performed in patients with documented CNS bleeding at APL diagnosis or during induction therapy.

Triple intrathecal chemotherapy will be administered (Methotrexate 12 mg + Ara-C 30 mg + Hydrocortisone 20 mg) on day 1 of cycles 2 and 3 of consolidation, and before starting the first maintenance cycle (in total, 3 lumbar punctures). If lumbar puncture is not possible, craniospinal radiotherapy can be administered.

7.3. Maintenance treatment.

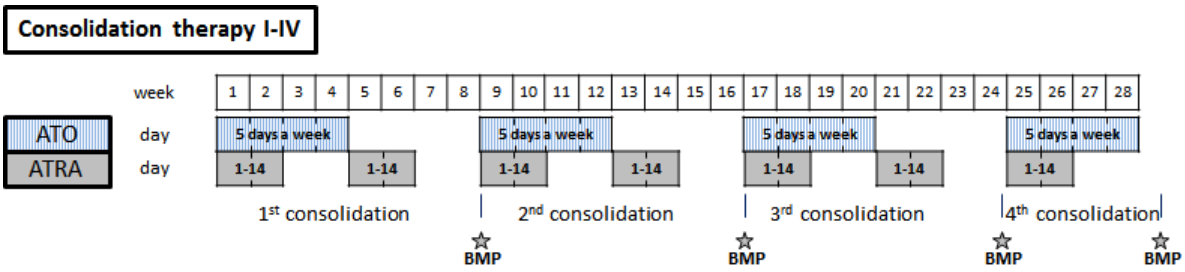
In all patients treated using the ATRA + chemotherapy scheme, two maintenance cycles with ATO + ATRA will be administered (if, for logistical reasons, there was no ATO available for these 2 maintenance cycles, it will be replaced by a 2-year maintenance with ATRA + 6-MP + MTX, see PETHEMA protocol LPA2012). Maintenance beginning between 2 and 4 weeks after haematological recovery of the final consolidation cycle (neutrophils ≥ 1.0 $x10^9$/L and platelets ≥ 100 $x10^9$/L). Each maintenance cycle should be initiated if the hematological recovery between cycles allows it. Full ambulatory management is recommended, to be admitted to hospital only if the clinical situation requires it.

Consider a central venous device (PIC, Hickman, or other) according to each particular case. A supplement with magnesium should be considered (300-600 mg / day orally divided into 2-3 doses or ampoules of 1.5 gr / 12 meq IV 1-3 times a day).

Two cycles of ATO + ATRA (total 12 weeks):

- ATO 0.15 mg / kg / day IV infusion for 2 hours, 5 days a week, resting on weekends, for 4 weeks. Rest 2 weeks between cycle and cycle.
- ATRA 45 mg / m² / day oral divided into two doses, for 2 weeks without interruption, resting 2 weeks, for 12 weeks. In those under 20 years of age, the dose of ATRA will be reduced to 25 mg / m²/ day fractioned into 2 doses.

Figure 2: Schematic view of maintenance:



Note: Between 67 and 80 kg of weight, a fixed dose of ATO of 10 mg / day (1 vial) can be administered. In the rest of the patients, the exact dose of 0.15 mg / kg / day (never exceeding 20 mg / day) is recommended.

MAINTENANCE treatment				
Drug	Dose	Via	Administration	Comments
ATO	0.15 mg / kg	iv for 2 h	Daily for 5 consecutive days of the week; therapeutic rest on days 6 and 7	4 weeks of treatment followed by 4 weeks without treatment, in a total of 2 cycles.
ATRA	45 mg / m^2	vo in two unique doses	Daily	2 weeks of treatment followed by 2 weeks without treatment, uninterrupted until the end of the second cycle of ATO; the doses will be rounded to the nearest multiple of 10.

7.3.1. Maintenance modifications

In case of significant and sustained myelotoxicity during the consolidation treatment (neutrophils <1 x 10 9 / L and / or platelets <50 x 10 9 / L for > 6 weeks after the start of a cycle), treatment should be reduced according to with section 8.1.3.

8 ATO + ATRA SCHEME

8.1. Induction Treatment

See instructions in section 6.

8.1.1. Induction Scheme: ATO + ATRA:

Holo-trans retinoic acid, will be administered orally from the first day at a dose of 45 mg / m² / day (rounded up to the nearest multiple of 10 above) fractionated into 2 doses.

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

- Treatment with ATRA will continue until CR is achieved (advisable for a minimum of 28 days) or for a maximum of 60 days in case of persistence of atypical promyelocytes in the bone marrow.

ATO at the dose of 0.15 mg / kg / day, from day 1 by intravenous continuous 1-2 hours infusion.

Treatment with ATO will continue until obtaining the CR (and recommendable for a minimum of 28 days) or up to a maximum of 60 days in case of persistence of atypical promyelocytes in the bone marrow.

INDUCTION treatment				
Drug	*Dose*	*Via*	*Administration*	*Comments*
ATO	*0.15 mg / kg*	*iv for 2 h*	*Daily for 5 consecutive days of the week; therapeutic rest on days 6 and 7*	*Start on day 1 until achieving the hematological CR / iCR, maximum until day 60.*
ATRA	*45 mg / m 2*	*vo in two unique doses*	*Daily*	*It is mandatory to start on day 1 of the induction treatment and until achieving the hematological CR / iCR, max. until day 60; rounded to the nearest multiple of 10.*

ATRA should be initiated at the minimum suspicion of APL, while ATO can be started with diagnostic confirmation. Modifications of the dose in case of toxicity should be carried out in accordance with section 8.1.3 The dose of ATRA should be reduced to 25 mg / m^2 in patients of age below 20 years.

Note: Between 67 and 80 kg of weight a fixed dose of ATO of 10 mg / day (1 vial) can be administered. In the rest of the patients, an exact dose of 0.15 mg / kg / day (never exceeding 20 mg / day) is recommended.

8.1.2. Support Measures in Induction

Cytoreduction: it is recommended to administer oral hydroxyurea (initial dose 2 g / day, adjusted according to leukocyte counts, up to 6 grams per day) to patients with leukocyte counts greater than $10x10^9$ / L or in case if this leukocyte counts are present during the first

weeks of induction. In those patients with significant leukocytosis (> 50 x10^9/ L) accompanied by differentiation syndrome with criteria of severity, it is recommended to administer 1 or 2 doses of Idarubicin, 12 mg / m² for the control of leukocytosis.

Prednisone: 0.5 mg / kg / day for the first 14 days from the start of ATRA in all patients.

Antibacterial and antifungal prophylaxis: it is recommended to administer ciprofloxacin 500 mg / 12h and fluconazole 100 mg / 24h VO from the start of chemotherapy to recovery of neutrophil count > 0.5-1 x 10^9 / L.

Hydration: taking into account the high risk of liquid retention in these patients (frequent blood product transfusions, differentiation syndrome) and the low rate of chemotherapy-related nephrotoxicity, a not excessive hydration is recommended (maximum 1.5 l / m^2 / day).

Electrolytes: to prevent the lengthening of the QTc, it is recommended to supplement with magnesium sulfate IV 1.5 grams every 12-24 hours in the hydration of the patient, at least while hospitalized. If it were necessary at discharge, the patient could take magnesium orally. It is also possible to supplement with potassium 40-80 meq / day IV to prevent alterations of the heart rhythm. Calcemia and pH / serum bicarbonate monitoring is also required, with corrections if necessary.

Transfusion: of platelet concentrates to maintain counts above 30x10^9 / L during the first 10 days and packed red blood cells (PRC) to maintain hemoglobin levels above 9 g / dL (5.5 µmol / l). In patients with a very high risk of fatal bleeding (hyperleukocytosis > 10 x 10^9 / L, or abnormal creatinine, or consumption coagulopathy, defined as the presence of hypofibrinogenemia or prolonged APTT, thrombin time, or prothrombin time, together with elevation of D-dimers or fibrinogen degradation products) platelets transfusion should be given for achieving more than 50 x 10^9 / L.

In all patients the hemostatic parameters should be corrected with fibrinogen or cryoprecipitate (to maintain serum fibrinogen higher than 150 mg/dL) and/or plasma (to maintain a Quick Index above 60% or INR under 1.3). In patients with severe differentiation syndrome and/or liquid overload, prothrombin complex concentrate can be administered instead. Nevertheless, signs and symptoms of thrombosis should be guarded. The use of recombinant FVII should be restricted to patients with refractory coagulopathy (not corrected in spite of the standard support measures previously described) who also present potentially lethal bleedings.

Anticoagulant measures: the use of heparin and antifibrinolytics are not recommended as prophylaxis. In case of severe venous or arterial thrombosis the patients will require

heparin and/or fibrinolytics, but the elevated bleeding risk should be taken into account if they present coagulopathy and/or platelet counts under 50 x 109/L. If a thrombotic /ischemic cerebrovascular accident takes place, in which the bleeding transformation would be life threatening, anticoagulation should be postponed until the resolution of the coagulopathy.

Growth factors: the use of granulocytic colony growth factors is not recommended during induction (they will only be allowed in case of severe neutropenia and life threatening infection at the same time).

8.1.3. Modification of the dose of ATRA and / or arsenic trioxide during the induction treatment

The treatment with ATO and/or ATRA may be temporarily withdrawn when the following complications arise:

Pseudotumor cerebri syndrome: Its incidence can be up to 13% in pediatric patients, and up to 5% in adults aged <25 years. It manifests with headache, nausea, vomiting and blurred vision (signs of endocranial hypertension), in the absence of space-occupying lesion. It is often necessary to temporarily stop treatment with ATRA and administer opioid analgesics and osmotic diuretics (acetazolamide). As soon as the patient's symptoms and clinical situation improve, treatment with ATRA should be resumed. If symptoms persist it may be necessary to reduce the ATRA dose by 50%.

Hepatotoxicity: Grade 3-4 hepatotoxicity (liver enzymes and / or bilirubin) has been observed in less than 5% of patients treated with ATRA or ATO separately, but its incidence increases up to 30% when concomitant treatment is given (counting induction and consolidation), being reversible with the temporary suspension of the ATO and / or ATRA. The occurrence of grade 3/4 hepatotoxicity forces a temporary suspension of treatment with ATO (temporary suspension of ATRA treatment may also be considered, but is not recommended during induction). As soon as the levels of serum bilirubin and / or GOT / GPT and / or alkaline phosphatase have decreased to < 4 times the upper limit of normal, treatment with ATO and / or ATRA should be resumed at 50% of the previous dose during the first 7 days. Then, in the absence of worsening of the previous toxicity, treatment with ATO and / or ATRA should proceed with the full dose.

Differentiation syndrome (DS):

It is mandatory to resort to prophylaxis with prednisone in a dose of 0.5 mg / kg / day VO during the first three weeks of induction. During treatment with holo-transretinoic acid (ATRA) and / or ATO, differentiation syndrome (DS) can develop rapidly. Your diagnosis

must be confirmed clinically. This syndrome should be suspected in the presence of any of these signs and symptoms (without definitive alternative cause to explain them): respiratory distress, hypoxemia, pulmonary infiltrates, pleural or pericardial effusion, hypotension, peripheral edema or weight gain, with or without presence of hyperleukocytosis. In this case the following measures should be adopted immediately:

- **Dexamethasone**, 10 mg/12 h IV for a minimum of 3 days and until the signs and symptoms of the differentiation syndrome disappear.
- In some cases the administration of furosemide is necessary
- Temporary withdrawal of ATRA treatment in those cases of severe differentiation syndrome.13 Serious DS is considered when at least 3 of the following criteria are presented:

1-Dyspnea / hypoxemia

2-Unexplained fever

3-Interstitial lung infiltrates (or intersitioalvelares)

4-Pleural or pericardial effusion

5-Arterial hypotension

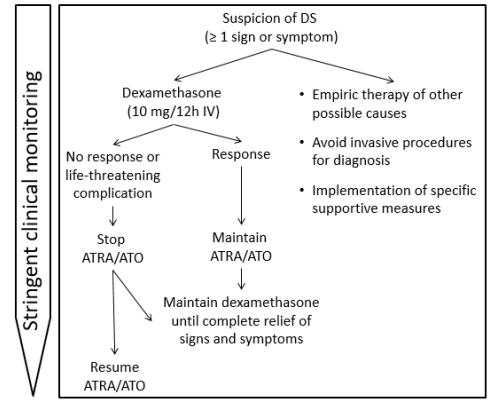
6-Acute kidney failure

7-Weight gain > 5kg (or > 10% basal weight)

Closely monitoring of vital signs and early transfer of APL patients to the ICU should be considered in case of diagnosis of severe differentiation syndrome. As soon as the patient's clinical situation improves and the symptoms have disappeared, treatment with ATRA and/or ATO should be resumed. In the absence of worsening of the previous toxicity, treatment with ATRA and/or ATO should continue with the full dose.

As soon as the patient's symptoms and clinical condition improve, treatment with ATRA can start again immediately.

Figure 3: Algorithm of DS management (adapted from Sanz et al).



Extended QTc interval

A prolongation of the QT interval in the ECG has been observed during treatment with ATO. This can lead to ventricular tachycardia (torsades de pointes), with fatal outcome. In this context, the possible interaction with other medications that prolong the QT interval should also be taken into account. For this reason, it is necessary to closely monitor the ECG and electrolytes during treatment with ATO. In particular, the levels of Mg ++ and K + should always be maintained in the high-normal range, taking into account possible concomitant treatments that deplete electrolyte levels (eg, amphotericin B, furosemide, etc.). Other drugs that significantly prolong QTC (such as triazoles, which can also inhibit ATRA metabolism) should also be avoided as much as possible. In the ECG, the QT interval is represented by the QRS complex, the ST segment and the T wave. Its measurement ranges from the lowest point of the Q wave to the end of the T wave. This interval depends to a great extent on the rhythm and several formulas have been proposed to adjust the QT interval to the cardiac rhythm in order to obtain the corrected QT interval (QTc); however, none of these proposed formulas is satisfactory. Despite this, data from existing medical journals indicate that one of the simplest methods for adjusting the QT interval to heart rhythm is the Fridericia formula.

QTc = QT / RR cubic root

In order to obtain greater precision, the QT interval must be measured in several consecutive ECGs and several successive beats to then obtain an average value for each ECG. The average QT value obtained is the one that must be used in the previous formula, in which all

measurements must be expressed in milliseconds (ie: 0.470 s = 470 msg). With the application of this formula, a QTc interval> 500 msg should be considered prolonged (in both sexes).

If a prolonged QTc interval (> 460 msg) is observed, close monitoring of the ECG and an urgent correction of the electrolytes (potassium, magnesium and calcium) will be necessary. Drugs that prolong the QTc interval should be avoided. The addition of magnesium sulfate supplements (ampoules of 1.5 mg for IV administration) can help prevent the development of fatal arrhythmias (Torsades des pointes).

If the QTc interval is> 500 msg the treatment with ATO should be interrupted, as well as the administration of any medication known to prolong the QTc interval, and the electrolytes have to be replenished. The time elapsed between the interruption of treatment with ATO and the normalization of the QTc interval can be several days. Once the QTc interval has normalized, treatment with ATO should be resumed at a dose of 0.075 mg / kg / day (50%) for the first 7 days and then, if no further prolongation occurs, continue at a dose of 0.10. mg / kg during a second week. Subsequently, if prolongation does not occur, treatment with ATO should continue with the full dose.

In case of renal failure, it must be taken into account that the arsenic trioxide will be eliminated more slowly.

More information on the properties and side effects of the ATO is given in section 12.5.

Haematological toxicity grade 3 or 4 attributable to arsenic trioxide

In case of significant myelotoxicity (neutrophils <1 x 10 9 / L and / or platelets <50 x 10 9 / L beyond day 35 after the start of induction), treatment with ATO should be discontinued. The ATRA will be maintained and a medullary aspirate will be programmed for the evaluation of the response once the cytopenias improve, with the ATRA suspended once the morphological RC has been objectified. It must be borne in mind that, especially in elderly patients, morphological findings in the bone marrow similar to arsenic poisoning (SMD-like) can occur.

Non-haematological toxicity grade 3 or 4 attributable to arsenic trioxide

The suspension of the ATO should be considered, always taking into account the risk benefit ratio. In case of non-haematological ATO toxicities (grade 3/4 toxicities according to the CTCAE classification, version 4.0), the treatment should be temporarily interrupted. As soon as the symptoms and clinical situation of the patient improve to < grade 2, treatment with ATO should be resumed with 50% of the previous dose during the first 7 days.

Then the ATO will be restarted with a 50% dose reduction. If the toxicity event does not return within three days of restarting the treatment with the reduced dose, in the absence of

worsening of the previous toxicity, treatment with ATO should proceed with 100% of the original dose. In case of recurrence of symptoms, treatment with ATO should be reduced to the previous dose or temporarily discontinued.

In case of clinical signs of ATO overdose, dimercaprol or penicillamine can be administered.

More information on the properties and side effects of the ATO is given in section 12.5.

8.2. Consolidation treatment

The induction treatment is followed by 4 cycles of consolidation with ATO / ATRA. Patients who achieve CR, once hematological recovery has occurred (PMN> 1 x10 9 / l and platelets> 100 x10 9 / l), will receive 4 successive cycles of consolidation with ATO + ATRA. In case of morphological CR with complete hemogram regeneration, the consolidation treatment should be initiated within 2-4 weeks after the documented CR. The cycles will be administered with a monthly interval if the hematological recovery between cycles allows it. In case of significant and sustained myelotoxicity during the consolidation treatment (neutrophils <1 x 10 9 / L and / or platelets <50 x 10 9 / L for> 6 weeks after the start of a cycle), treatment should be reduced according to with section 8.1.3.

Full ambulatory management is recommended, with administration of chemotherapy in the day hospital, and admission only if the clinical situation requires it.

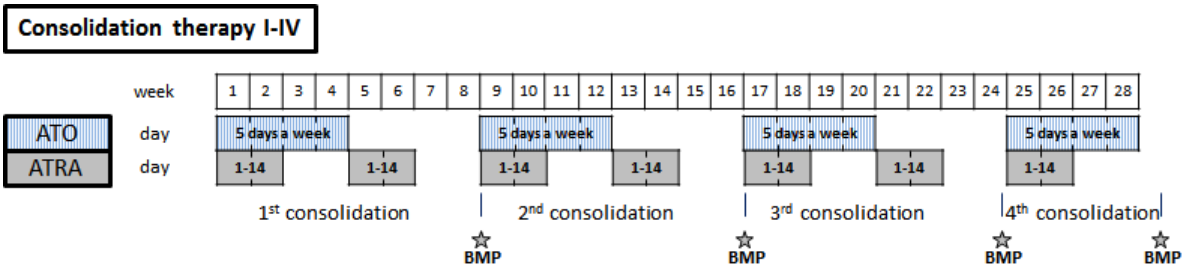
Consider a central venous device (PIC, hickman, or other) according to each particular case. Supplement with magnesium (300-600 mg / day orally divided into 2-3 doses or ampoules of 1.5 gr / 12 meq IV 1-3 times a day).

Antibacterial and antifungal prophylaxis: it is recommended to administer ciprofloxacin 500 mg / 12h and fluconazole 100 mg / 24h VO from the start of the ATO to the recovery of neutrophil count> 0.5-1 x 10 9 / L.

Four cycles of ATO + ATRA:

- ATO 0.15 mg / kg / day IV in infusion for 2 hours, 5 days a week, resting on weekends, for 4 weeks.
- ATRA 45 mg / m^2 / day oral divided into two doses, for 2 weeks without interruption, resting 2 weeks, for 28 weeks. In those under 20 years of age, the dose of ATRA will be reduced to 25 mg / m^2 / day divided into 2 doses.

Figure 4 Schematic view of consolidation.



Note: Between 67 and 80 kg of weight a fixed dose of ATO of 10 mg / day (1 vial) can be administered. In all other patients, an exact dose of 0.15 mg / kg / day (never exceeding 20 mg / day) is recommended.

CONSOLIDATION treatment (4 cycles)				
Drug	*Dose*	*Via*	*Administration*	*Comments*
ATO	*0.15 mg / kg*	*iv for 2 h*	*Daily for 5 consecutive days of the week; therapeutic rest on days 6 and 7*	*4 weeks of treatment followed by 4 weeks without treatment, in a total of 4 cycles.*
ATRA	*45 mg / m 2*	*vo in two unique doses*	*Daily*	*2 weeks of treatment followed by 2 weeks without treatment, uninterrupted until the end of the fourth cycle of ATO; the doses will be rounded to the nearest multiple of 10.*

8.2.1. Dose modification during consolidation treatment

8.2.1.1. Modifications of the ATRA dose.

The treatment with ATRA will be temporarily withdrawn when the following complications arise:

Pseudotumor cerebri syndrome: see section 8.1.3.

Hepatotoxicity: see section 8.1.3.

Once CR is achieved, DS is not expected.

8.2.2.2. Modifications of the ATO dose.

Hepatotoxicity: see section 8.1.3.

QTc prolongation: see section 8.1.3.

Haematological toxicity grade 3 or 4: see section 8.1.3.

Once CR is achieved, DS is not expected.

8.2.2. Prophylaxis of CNS relapse with intrathecal chemotherapy in patients with CNS bleeding at APL diagnosis or during induction therapy

It should only be performed in patients with documented CNS bleeding at APL diagnosis or during induction therapy.

Triple intrathecal chemotherapy will be administered (methotrexate 12 mg + Ara-C 30 mg + hydrocortisone 20 mg) on day 1 of cycles 2 and 3 of consolidation, and before beginning the first maintenance cycle (in total, 3 lumbar puncture). If the lumbar puncture is not possible, craniospinal radiotherapy can be administered.

9. 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 BM aspirate and biopsy. Extramedullary sites known to be involved by leukemia prior to treatment (e.g., mediastinal lymphadenopathy or cerebrospinal fluid (CSF)) must be reexamined as well. Immunophenotyping, cytochemistry, and cytogenetic analyses are supportive data but are not required for clinical assessment. Investigators are cautioned that the BM cytology and PB 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 BM examination should be performed at least one week later: confirmatory data should be gathered from cytogenetic analyses, inmunophenotyping, or cytochemistry.

9.1. Complete Remission (CR)

Requires all of the following:

- PB Counts:
  - ANC >1.5x10^9/l
  - Platelet count > 100x10^9/l
  - No leukemic blasts or atypical promyelocytes in the PB.
- BM aspirate:
  - Not hypoplastic sample
  - ≤ 5% blasts or malignant promyelocytes
  - No extramedullary leukemia, such as CNS or soft tissue involvement.

9.2. Treatment Failure

9.2.1. 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 to the Study Chair before making therapeutic decisions based on this observation[1]. Final differentiation of promyeloblasts can take even 60 days on ATRA therapy[2].

[2] Morphological features in BM aspirates performed early during induction therapy may lead to erroneously labeling some individual patients showing delayed maturation features and/or persistence of atypical promyelocytes as resistant. These findings, which are occasionally detectable several weeks after the start of treatment (up to 40-50 days), should in no way lead to therapeutic 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.

9.2.2. Treatment Failure due to death of the patient during induction therapy:

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

9.3. Relapse

Relapse following complete remission is defined as:

9.3.1. Hematological relapse:

> 20% of blasts/atypical promyelocytes in a unique BM sample or more than 5% of blasts/atypical promyelocytes in two BM samples separated by a week is necessary to meet the criteria for relapse. Genetic confirmation should be performed with any of the methods described in Sections 4 and 5.

9.3.2. 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.

9.3.3. Molecular relapse:

This is defined as the reappearance of PCR positivity in 2 consecutive BM samples at any time after the end of the therapy. PCR positivity is defined as the reappearance of the PML/RARα rearrangement, using an RT-PCR assay with a sensitivity level of 10^{-4}. A positive PML/RARα by RT-PCR at the end of treatment (molecular persistence) or at any time during follow up (molecular relapse) must always be confirmed in a new BM sample collected within the following 2 weeks and sent to a Reference Laboratory (Plataforma LMA – PLATAFO-LMA)

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9.4. Definition of long-term events

9.4.1. Overall survival

This is defined as the time from inclusion in the protocol to death from APL or toxicity of the treatment.

9.4.2. Disease free survival

This is defined as the time after CR is achieved to APL relapse being observed (see section 8.3).

9.4.3. Event free survival

This is defined as the time from inclusion in the protocol to APL relapse, secondary neoplasm or death from treatment toxicity.

10. CLINICAL AND ANALYTICAL MONITORING: ATRA + CHEMOTHERAPY

Tests & Observations	***Prior to Study***	***Induction***	***Prior to Each Consolidation Cycle***			***During Each Consolidation Cycle***			***Maintenance***	***Follow-Up****
			C1	*C2*	***C3***	***C1***	***C2***	***C3***		
History/Physical exam	***X***	***Daily***	***X***	***X***	***X***	*Weekly*	*Weekly*	*Weekly*	*Weekly*	***X***
Height/Weight/BSA	***X***	***Daily***	***X***	***X***	***X***	*Weekly*	*Weekly*	*Weekly*	*Weekly*	***X***
*Performance status***	***X***		***X***	***X***	***X***	*Weekly*	*Weekly*	*Weekly*	*Weekly*	***X***
*Pregnancy test****	***X***									
Blood counts	***X***	***3x/week+***	***X***	***X***	***X***	*Weekly*	*Weekly*	*Weekly*	***Weekly***	***X***
Prothrombin time, APTT, Thrombin time, Fibrinogen and PDF or PDX or D dimmers	***X***	*3x/week+*	***X***	***X***	***X***	*Weekly*	*Weekly*	*Weekly*	***X***	***X***
Serum biochemistry: Glucose, Creatinine, Uric Acid, Bilirubin, Alkaline Phosphatase, LDH, AST, ALT, electrolytes, Calcium, Phosphorus	***X***	*3x/week+*	***X***	***X***	***X***	*Weekly*	*Weekly*	*Weekly*	***Weekly***	***X***

Cholesterol, Triglycerides,	***X***	***Weekly***	***X***	***X***	***X***				***Monthly***	***X***
Total Proteins, and Albumin										
LVEF (Echo or MUGA) (optional)	***X***		***X***						***A***	***A***
BM Aspirate	***X***	***B***	***X***						***E***	***E***
Karyotype	***X***	***C***								
RT-PCR	***X***	***C***							***E***	***E***
Immunophenotype	***X***									
ECG with QTc	***X***								***F***	

* 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 PB 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 or twice annually for 10 years.

B The first needle aspiration will be done when clear signs of recovery are observed in blood counts and PB criteria for CR are met, but never before day 30 after ending chemotherapy, and repeated q 1-2 weeks until BM criteria for CR are met. BM 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 some individual patients showing delayed maturation features and/or

persistence of atypical promyelocytes as resistant. 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 therapeutic 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 cytogenetic 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 Every 6-12 months until completing 2 years since the finishing of the treatment (in low and intermediate risk patients). Every 3-6 months until completing 2 years since the finishing of the treatment (in high risk patients).

F Perform 1 or 2 times per week if the patient receives ATO. Perform daily if the patient is treated with ATO and has a prolonged QTc (until it is corrected); or if the patient has a significant cardiological history (especially in the presence of ventricular arrhythmias) or other risk factors (concomitant use of drugs that prolong QTc, electrolyte alterations).

Perform daily if the patient is treated with ATO and has a prolonged QTc (until it is corrected); or if the patient has a significant cardiological history (especially in the presence of ventricular arrhythmias) or other risk factors (concomitant use of drugs that prolong QTc, electrolyte alterations). PRN: According to medical indications.

11. CLINICAL AND ANALYTICAL MONITORING: ATO + ATRA

Tests & Observations	***Pre-treatment***	***Induction with ATO + ATRA £***	***Consolidation with ATO + ATRA***	***Follow-up***
HLA typing	*x*			
Donor searching#	*x*			
History/Physical exam	*x*	***Daily£***	***Weekly***	***X***
Height/Weight/BSA	*x*	***Daily£***	***X***	***X***
*Performance status***	*x*		***x***	***X***
*Pregnancy test****	*x*		***x***	***X****
Blood counts	*x*	***3x/week+***	***Weekly***	
Prothrombin time, APTT, Thrombin time, Fibrinogen and PDF or PDX or D dimmers	*x*	***3x/week+***	***PRN***	***PRN***
Serum biochemistry: Glucose, Creatinine, Uric Acid, Bilirubin, Alkaline Phosphatase, LDH, AST, ALT, electrolytes, Calcium, Phosphorus	*x*	***3x/week+***	***Weekly*** ***A***	***PRN***
*ECG****	*x*	***A***	***A***	***PRN***
BM Aspirate	*x*	***C***	***E***	***F***
Karyotype	*x*	***D***		
RT-PCR	*x*	***D***	***E***	***F***

Immunophenotype	*x*			
LVEF (Echo or MUGA) (optional)	*x*		***G***	***G***

X To be done

£ Patients with molecular relapse of APL can receive induction therapy in an outpatient clinic

If a patient is a potential candidate for alo-HSCT

If the patient is a potential candidate for auto-HSCT

* 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 PB counts.

** WHO system of assessment

*** In women with reproductive potential

**** ECG – electrocardiogram with QTc corrected analysis

+ Daily during the first 1-2 weeks

A Perform 1 or 2 times per week if the patient receives ATO. Perform daily if the patient is receiving ATO and has a prolonged QTc (until it is corrected); or if it has a significant cardiological history (especially in the presence of ventricular arrhythmias) or other risk factors (concomitant use of drugs that prolong QT, electrolyte alterations).

B Perform daily if the patient is receiving ATO and has a prolonged QTc (until it is corrected); or if you have a significant cardiac history or other risk factors for performing arrhythmias.

C The first bone marrow aspiration should be performed when there are clear signs of hemopoietic recovery in the peripheral blood counts and CR criteria are met, but never before 30 days from the start of ATO. These will be repeated until CR criteria are met in bone marrow.

D An early molecular and cytogenetic evaluation can also lead to a misinterpretation, in addition to not being informative with respect to the subsequent clinical course.

E Coinciding with the recovery of hemoperipheral counts after cycle 4 of consolidation.F Every 6-12 months until the end of 2 years from the end of treatment in low and intermediate risk patients .Every 3 -6 months until the end of the 2 years since the completion of high-risk treatment.

G At the end of the consolidation 4 .Then repeat biannually for 10 years.

12. FORMULATION AND MODE OF ADMINISTRATION OF DRUGS

12. 1. ATRA

12.1.1. Other names

Tretinoin, Holo-transretinoic acid, Vesanoid.

12.2.3. Classification

Differentiation inducing agent, noncytotoxic.

12.2.4. Action mode.

Tretinoin is a natural metabolite of retinol and belongs to a class of retinoids, which are structurally related to vitamin A and involved in the regulation of various biological processes. This 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 in a place protected from light.

12.1.5. Administration.

Orally. 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:

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

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

However, to date there are no data to suggest that these medications increase or decrease the efficacy or toxicity of ATRA.

12.1.7. Obtaining

Commercially available for oral use in 10 mg capsules.

12.1.8. Side effects

The side effect of systemic retinoid therapy closely resemble those of hypervitaminosis A syndrome. A list of 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%)		E		
Blood/BM febrile neutropenia	basophilia (severe, rare)		E		
	hyperleukocytosis (75%)	I	E		
Cardiovascular (general)	pericarditis (6%)		E	D	
	edema (> 25%)		E		
Coagulation	thrombosis/embolism (8%)		E	D	
Constitutional symptoms	fatigue (> 25%)		E		
	fever (> 25%)	I	E		
	shivering (> 25%)	I	E		
	weight gain (32%)		E		
Dermatology/skin	cheilitis (24-65%)		E		
	mucosal and skin dryness (24-65%)		E		
	photosensitivity (rare)	I	E		
	pruritus/rash (24-65%)		E		
Gastrointestinal	*emetogenic potential:* rare				
	gastritis (rare)		E		
	nausea/vomiting (51%)	I	E		
Bleeding	dermal bleeding (> 25%)		E		

Hepatic	elevated bilirubin (16%)		E		
	elevated hepatic enzymes (> 25%)		E		
Lymphatics	cervical/tonsillar lymphadenopathy (10%)		E		
Metabolic/laboratory	hypercalcemia (rare)		E		
	hypercholesterolemia (> 25%)		E		
	hyperhistaminemia (rare)		E		
	hyperlipidemia (rare)		E		
	hypertriglyceridemia (> 25%)		E		
Ocular/visual	visual disturbance, photophobia, conjunctivitis (rare)		E		
Pain	abdominal pain (> 25%)		E		
	arthralgia (20-30%)		E		
	back pain (> 25%)		E		
	bone pain (20-30%)		E		
	chest pain (> 25%)		E		
	headache (29-90%)	I	E		
Pulmonary	coughing (> 25%)		E		
	dyspnea (> 25%)		E		
	nasal congestion (24-65%)		E		
Renal/genitourinary	increased serum creatinine (20-56%)		E		
Sexual/reproductive function	penile or scrotal ulceration (rare)		E		

Síndromes	pseudotumor cerebro (rare)	I	E		
	retinoic acid syndrome (25%)	I	E		
	Sweet's syndrome (rare)		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 bleeding, 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 has 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 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 (e.g., 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.

12.1.7. 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 for 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 patient IV site through the side arm of a running IV over 5-20 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 patient 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 vials 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 arrhythmias 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 antiemetic therapy 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 g, and 2 g 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. Arsenic trioxide

12.5.1. Other names

Trisenox, ATO.

12.5.2. Classification

Antineoplastic (differentiating and pro-apoptotic agent).

12.5.3. Mode of action

The exact mechanism of action is still largely unknown. In vitro trisenox induces blastic differentiation and fragmentation of DNA in APL cells. Moreover, ATO causes damage and degradation of the PML / RARα fusion protein.

12.5.4. Storage and Stability

Liver metabolism. In the liver, the pentavalent arsenic molecule is reduced to trivalent arsenic (active metabolite) by the enzyme arsenate reductase. At the same time, the arsenic trioxide is converted into dimethylarsenic by methyltransferases and is excreted in the urine as dimethylarsenic acid.

12.5.5. Preparation

In Europe, ATO is approved for the treatment of relapsed APL and for the treatment of newly diagnosed intermediate and low risk APL (first line). ATO is commercially available for IV injection (1 vial of 10 mL contains 10 mg of ATO). ATO is reconstituted in 100-200 mL of SG 5% or SF 0.9%. It must be administered immediately after reconstitution. The part of the unused vial must be discarded.

12.5.6. Administration

The solution should be administered slowly IV (1-2 hours). If vasomotor reaction occurs with the infusion, this can be done up to a maximum of 4 hours.

12.5.7. Incompatibilities

Drugs producing hypokalemia or hypomagnesemia, as loop diuretics, foscarnet and amphotericin B, should be used with caution. Concomitant use of drugs that prolong the QT interval, such as: antiarrhythmics (aprindine, amylobin, B-blockers such as sotalol,

amiodarone, diltiazem, disopyramide, flecainide, phenothiazines, lidocaine, propafenone, procainamide, quinidine), some quinolones (especially moxifloxacin), cisapride, thioridazine, macrolides, antihistamines H1 (astemizole, terfenadine), ketaconazole, tricyclic antidepressants, fluoxetine and other serotonin reuptake inhibitors, phenytoin, antivirals (efavirenz, indinavir, ritonavir, saquinavir) and pimozide, should be avoided.

The concomitant administration of N-acetylcysteine should be avoided as it may decrease the effect of ATO by increasing the concentration of glutathione. Seafood and some herbal products should be avoided since they contain arsenic.

12.5.8. Side effects

– Cardiovascular: tachycardia, edema, QTc> 500 msec (30%), chest pain, hypotension (<10%).

– Central nervous system: headache (50%), insomnia, anxiety, depression, tremor (20%), seizures, drowsiness, agitation, confusion, coma (<5%).

– Dermatological: rash; itching (30%), hyperpigmentation, local reaction (<20%).

– Gastrointestinal: nausea (75%), vomiting, abdominal pain, dry mouth, diarrhea, constipation.

– Metabolic: hypokalemia (50%), hypomagnesemia (45%), hyperglycemia, hyperkalemia.

– Hematological: leukocytosis (50%), differentiation syndrome (25%), thrombocytopenia (20%), anemia (15%), neutropenic fever (15%), neutropenia (10%).

– Hepatic: elevation of GOT and GPT (15-20%).

– Neuromuscular: arthralgias, cramps, paresthesias (30%), myalgia, bone pain (15%).

– Other: hypersensitivity (<5%), renal failure (<10%).

12.5.9. Pregnancy and lactation

Category D. This is contraindicated during pregnancy and lactation due to its possible teratogenicity. The use of effective contraceptive measures in case of women of childbearing age should be guaranteed.

12.5.10. Monitoring and special precautions

– Electrocardiographic monitoring (12 leads, measuring the QTc interval) and biochemical parameters (potassium, magnesium, calcium and creatinine). Perform before the

start of treatment and 1-3 times per week during treatment. Perform daily in patients with prolonged QTc or with predisposing factors to perform severe arrhythmias (basic heart disease, taking loop diuretics, foscarnet or amphotericin B, renal failure). Maintain the QTc interval <460 msec during treatment with ATO, due to the risk of ventricular tachyarrhythmia (Torsades des pointes, ventricular fibrillation) and complete atrioventricular block. Stop all drugs that prolong the QT interval and treatment with ATO if QTc> 460 msec. Magnesium and potassium should be corrected to obtain serum levels above 1.8 mg / dL and 4 mEq / L respectively. Administer magnesium and / or potassium IV supplements for the treatment / prophylaxis of ventricular arrhythmias.

– Control of morphology. During induction, especially in case of suspicion of differentiation syndrome or leukocytosis (> $5x10^9$/L) (see Sections 7.1.3 and 7.1.4).

– The safety profile for children under 5 is not known.

– Use with caution in case of renal failure.

– It may be necessary to administer thiamine supplements (vitamin B1) for the treatment / prophylaxis of neuropathy.

12.5.11. Treatment in case of overdose

Symptoms of overdose include seizures, confusion and muscle weakness. The treatment should be stopped and chelators started (dimercaprol 3 mg / kg IM every 4 hours until the vital risk disappears, and then continue with penicillamine 250 mg VO every 6-8 hours).

12.5.12. References

http://www.uptodate.com

13. REFERENCES

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2. 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/RARα-positive acute promyelocytic leukemia. Blood. 1999;94:3015-21.

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