

ACUTE PROMYELOCYTIC LEUKEMIA

MODIFIED AIDA INDUCTION REGIMEN (SANZ REGIMEN)

INDUCTION

Tretinoin (ATRA)	45 mg/m ² /day*	PO	Day 1 until CHR**
Idarubicin	12 mg/m ² /day	IV***	Days 2, 4, 6 and 8
Dexamethasone	10 mg Q12H	IV	See below#

*Divided into 2 daily doses each 12 hours apart. In patients younger than 15 years, the dose of tretinoin was reduced to 25 mg/m²/day; **Administer the tretinoin until complete hematological response and for a maximum of 90 days; ***Administer over 15 – 30 minutes; #At the first signs of suspected APL syndrome, ATRA was discontinued and patients were given dexamethasone every 12 hours. Prophylactic dexamethasone (in the same doses) was also administered in cases where the WBC was greater than 5 x 10⁹/L.

CONSOLIDATION: For patients in complete hematological remission only. Each 28 days in duration.

CONSOLIDATION COURSE 1

Idarubicin	5 mg/m ² /day	IV	Days 1 – 4
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CONSOLIDATION COURSE 2

Mitoxantrone	10 mg/m ² /day	IV	Days 1 – 5
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CONSOLIDATION COURSE 3

Idarubicin	12 mg/m ²	IV	Day 1
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MAINTENANCE

For patients who are PCR negative for the PML-RAR α hybrid gene were started on maintenance therapy.

6-Mercaptopurine	90 mg/m ² /day	PO	Daily
Methotrexate	15 mg/m ² /week	IM	Q week
Tretinoin (ATRA)	45 mg/m ² /day	PO*	For 15 days every 3 months

*Divided into 2 doses daily i.e., BID.

Maintenance therapy was continued for 2 years.

DOSE MODIFICATION: Doses of 6-Mercaptopurine and methotrexate were reduced by 50% if the WBC was lower than 3.5 x 10⁹/L, and discontinued if lower than 2.5 x 10⁹/L.

NOTE: See risk-adapted regimen for patients with intermediate and high risk disease.

Reference: [Sanz MA, et al. Blood 1999;94:3015 – 21.](#)

RISK ADAPTED AIDA INDUCTION REGIMEN (FOR INT. AND HIGH RISK PATIENTS)

Definition of risk:

Low risk: WBC count of less than $10 \times 10^9/L$ and a platelet count of more than $40 \times 10^9/L$.

Intermediate risk: WBC count of less than $10 \times 10^9/L$ and a platelet count of less than $40 \times 10^9/L$.

High risk: WBC count equal to or more than $10 \times 10^9/L$.

INDUCTION

Tretinoin (ATRA)	45 mg/m ² /day*	PO	Day 1 until CHR**
Idarubicin	12 mg/m ² /day	IVB***	Days 2, 4, 6 and 8 ^φ
Prednisone	0.5 mg/kg/day	PO	Days 1 – 15 [#]

*Divided into 2 daily doses, each 12 hours apart. In patients 20 years of age and younger, the dose of tretinoin was reduced to 25 mg/m²/day; **Administer the tretinoin until complete hematological response or for a maximum of 90 days; ***Administer over 15 – 30 minutes; ^φThe Day 8 idarubicin was omitted in patients older than 70 years of age; [#]At the first signs of suspected APL syndrome, ATRA was discontinued (and the prednisone) and patients were given dexamethasone 10 mg IV every 12 hours.

CONSOLIDATION: Courses 28 days in duration

CONSOLIDATION COURSE 1

Idarubicin	7 mg/m ² /day	IV	Days 1 – 4
Tretinoin (ATRA)	45 mg/m ² /day	PO*	Days 1 – 15

CONSOLIDATION COURSE 2

Mitoxantrone	10 mg/m ² /day	IV	Days 1 – 5
Tretinoin (ATRA)	45 mg/m ² /day	PO*	Days 1 – 15

CONSOLIDATION COURSE 3

Idarubicin	12 mg/m ² /day	IV	Days 1 and 2
Tretinoin (ATRA)	45 mg/m ² /day	PO*	Days 1 – 15

*Divided into 2 doses daily i.e., BID.

MAINTENANCE

For patients who are PCR negative for the PML-RAR α hybrid gene were started on maintenance therapy. Begin 3 – 4 weeks after hematological recovery from consolidation.

6-Mercaptopurine	50 mg/m ² /day	PO	Daily
Methotrexate	15 mg/m ² /week	IM	Q week
Tretinoin	45 mg/m ² /day	PO*	For 15 days every 3 months

*Divided into 2 doses daily i.e., BID.

Maintenance therapy was continued for 2 years.

DOSE MODIFICATION: Doses of 6-Mercaptopurine and methotrexate were reduced by 50% if the WBC was lower than $3.5 \times 10^9/L$, and discontinued if lower than $2.5 \times 10^9/L$.

Reference: [Sanz MA, et al. Blood 2004;103:1237 – 43.](#)

TRETINOIN (ALL TRANS RETINOIC ACID) – ARSENIC TRIOXIDE +/- GEMTUZUMAB

INDUCTION:

Low-risk patients (WBC less than $10 \times 10^9/L$):

Tretinoin (ATRA)	45 mg/m ² /day	PO*	Daily until near CR (see note)
Arsenic trioxide	0.15 mg/kg/day	IV**	Day 10 daily until near CR

High-risk patients ((WBC greater than $10 \times 10^9/L$):

Tretinoin (ATRA)	45 mg/m ² /day	PO*	Daily until near CR (see note)
Arsenic trioxide	0.15 mg/kg/day	IV**	Day 10 daily until near CR
Gemtuzumab‡	9 mg/m ²	IV	Day 1

*Divided into 2 doses daily i.e., BID; **Administer over 1 hour; ‡Routine premedication administered.

NOTE 1: APL differentiation syndrome was treated with 45 mg methylprednisolone daily for 7 days. Platelet transfusions were administered to maintain the platelet count greater than $30 \times 10^9/L$, and cryoprecipitate or fresh frozen plasma was administered to maintain serum fibrinogen above 150 mg/dL, and the INR less than 1.5.

NOTE 2: Weekly marrow aspirates performed beginning near day 25–28 of treatment. Tretinoin and arsenic discontinued when marrow showed less than 5% blasts and no abnormal promyelocytes. CR achieved and maintenance/consolidation began with above marrow findings plus neutrophils greater than $1 \times 10^9/L$ and platelets greater than $100 \times 10^9/L$.

MAINTENANCE/CONSOLIDATION:

Arsenic trioxide	0.15 mg/kg/day	IV	Monday – Friday of weeks 1 – 4, 9 – 12, 17 – 20, and 25 – 28
Tretinoin (ATRA)	45 mg/m ² /day	PO*	Daily during weeks 1 – 2, 5 – 6, 9 – 10, 13 – 14, 17 – 18, 21 – 22, and 25 – 26

*Divided into 2 doses daily i.e., BID.

NOTE: If either tretinoin or arsenic trioxide were discontinued, patients received gemtuzumab 9 mg/m² IV once a month until 28 weeks have elapsed from CR date.

DOSE MODIFICATIONS: The dose of tretinoin was reduced by 50% if grade 3 or 4 toxicity developed; and the drug was discontinued if toxicity persisted after dose reduction.

PATIENT MONITORING: CBCs were checked every 1 –2 months. RT-PCR (bone marrow) was performed at achievement of CR and then every 3 months thereafter for 2 years. If the RT-PCR was still positive 3 months after the CR date, a repeat test was performed 2 – 4 weeks later. The same procedure was followed if the PCR reverts to positive after being negative at 3 months. If a repeat PCR was confirmed positive, a diagnosis of molecular relapse should be made (or molecular failure if the test never became negative) and patients received gemtuzumab ozogamicin 9 mg/m² once monthly for 3 months while continuing tretinoin and arsenic trioxide (or resuming it if relapse occurred after discontinuation of therapy).

Reference: [Estey E, et al. *Blood* 2006;107:3469 – 73.](#)

RELAPSED APL

ARSENIC TRIOXIDE (AS₂O₃)

INDUCTION SCHEDULE

Arsenic trioxide 0.15 mg/kg/day IV* Daily until BM remission**

*Administer over 2 – 4 hours; **Total number of induction doses not to exceed 60 doses.

CONSOLIDATION SCHEDULE

Arsenic trioxide 0.15 mg/kg/day IV* Daily for up to 25 doses**

*Administer over 2 hours; **Administer for up to 25 doses. Doses may be given on consecutive days or on a schedule of daily Monday – Friday for 5 weeks. Start consolidation therapy 3 – 6 weeks after completion of induction therapy. May be repeated to a maximum of 6 courses.

Reference: [Soignet SL, et al. *N Engl J Med* 1998;339:1341 – 8.](#)

ACUTE PROMYELOCYTIC LEUKEMIA

CLINICAL TRIALS

IRB# 075-05

INDUCTION THERAPY

If WBC LESS than $20 \times 10^9/L$:

Tretinoin (ATRA)	45 mg/m ² /day*	PO	Days 1 – 60
Daunorubicin ¹	60 mg/m ² /dose	IV**	Days 4, 6, and 8

*Divide daily dose into two divided doses (i.e., 22.5 mg/m² Q12H). Dose to be rounded to nearest 10 mg dose; **Administer over 10 – 15 minutes.

NOTE: ¹If the WBC count increases to $20 \times 10^9/L$ prior to Day 14, add hydroxyurea (to maintain WBC less than $20 \times 10^9/L$ – recommended starting dose is 1500 mg PO Q6H) and dexamethasone (10 mg IV BID until WBC less than $20 \times 10^9/L$). If evidence of the APL syndrome or leukostasis, begin daunorubicin immediately.

If WBC $20 \times 10^9/L$ or GREATER¹:

Tretinoin (ATRA)	45 mg/m ² /day*	PO	Days 1 – 60
Daunorubicin	60 mg/m ² /dose	IV**	Days 4, 6, and 8
Hydroxyurea	Dose to maintain WBC less than $20 \times 10^9/L$ – recommended starting dose is 1500 mg PO QID.		
Dexamethasone	10 mg BID	IV	Days 1 – 14

*Divide daily dose into two divided doses (i.e., 22.5 mg/m² Q12H). Dose to be rounded to nearest 10 mg dose; **Administer over 10 – 15 minutes.

NOTE: ¹If evidence of the APL syndrome or leukostasis, begin daunorubicin immediately.

Disease assessment for clinical and molecular response between Day 60 and Day 67. If in CR or NR, then proceed to Module 2.

MODULE 2:

Cytarabine	667 mg/m ² /day	CIVI*	Days 1 – 3
Daunorubicin	60 mg/m ² /day**	IV***	Days 1 – 3
Arsenic trioxide	0.15 mg/kg/day****	IV	Day 8 (for 30 total doses)

*Administer as a continuous 24 hour infusion; **Dose reduced to 30 mg/m² per dose if LVEF is less than 45%; ***Administer over 10 – 15 minutes; ****Administer arsenic trioxide daily on Monday – Friday, starting Day 8, for a total of 30 doses.

Response assessment upon hematological recovery (between days 56 and 63). Patients not in clinical complete remission are OFF study. Patients in clinical and/or cytogenetic remission but NOT in molecular remission will proceed to Module 3. Patients in complete clinical remission will proceed to maintenance therapy.

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MODULE 3:

Arsenic trioxide 0.15 mg/kg/day**** IV Monday – Friday for 30 doses

****Administer arsenic trioxide daily on Monday – Friday, for a total of 30 doses.

MAINTENANCE THERAPY:

For patients in complete clinical remission the following treatment is required:

Patients with a presenting WBC of $10 \times 10^9/L$ or LESS:

Tretinoin (ATRA)	45 mg/m ² /day*	PO	For 15 days every 3 months
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Maintenance therapy continued for 2 years.

Patients with a presenting WBC of GREATER than $10 \times 10^9/L$ or Module 3 required (i.e., patients not in molecular remission):

Tretinoin (ATRA)	45 mg/m ² /day*	PO	For 15 days every 3 months
6-Mercaptopurine	90 mg/m ² /day	PO	Daily
Methotrexate	15 mg/m ² /week	PO	Q week

Maintenance therapy continued for 2 years.

*Divide daily dose into two divided doses (i.e., 22.5 mg/m² Q12H). Dose to be rounded to nearest 10 mg dose.

DOSE MODIFICATIONS FOR MAINTENANCE:

Tretinoin: no adjustment.

Methotrexate: If hepatic transaminases are greater than 100, hold until less than 2 x ULN, then reduce dose by 25%. Methotrexate dose should be reduced by 50% if ANC is between $1 \times 10^9/L$ and $1.5 \times 10^9/L$ and should be held for an ANC less than $0.1 \times 10^9/L$. Methotrexate dose should be reduced by 50% if platelets are between $50 \times 10^9/L$ and $75 \times 10^9/L$ and should be held for a platelet count of less than $50 \times 10^9/L$.

6-Mercaptopurine: 6-Mercaptopurine dose should be reduced by 50% if ANC is between $1 \times 10^9/L$ and $1.5 \times 10^9/L$ and should be held for an ANC less than $0.1 \times 10^9/L$. 6-Mercaptopurine dose should be reduced by 50% if platelets are between $50 \times 10^9/L$ and $75 \times 10^9/L$ and should be held for a platelet count of less than $50 \times 10^9/L$.

DEFINITIONS FOR RESPONSES:

CLINICAL: Complete response (CR) is defined as bone marrow cellularity of greater than 20% with less than 5% blasts, with peripheral blood ANC greater than $1.5 \times 10^9/L$ and platelets greater than $100 \times 10^9/L$ and the absence of detectable residual leukemia in the peripheral blood and extramedullary sites (including the CNS). Any patient surviving treatment but not achieving CR will be considered a non-response (NR).

MOLECULAR: Molecular remission will be defined as less than $1/10^4$ bone marrow cells expressing PML-RAR α transcript by standard qualitative RT-PCR. If PML-RAR α NQ in peripheral blood is greater than 10^{-6} , this should be considered potentially significant and lead to quantitative determination by standard RT-PCR on a BM aspirate.

CYTOGENETIC: Cytogenetic remission will be defined as zero metaphases demonstrating t(15;17) cytogenetics and/or no significant increased above baseline in FISH signals signifying PML-RAR α .

Reference: IRB# 075-05