

SWOG S0535: A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients With Previously Untreated High-Risk Acute Promyelocytic Leukemia

Fast Facts

ELIGIBILITY CRITERIA

Initial Registration:

1. Patients must have a morphologically confirmed diagnosis of high risk (see Section 4.2c) acute promyelocytic leukemia (APL), based on bone marrow examination performed within 14 days before registration. The WBC confirming high risk must be obtained within 14 days prior to registration.
2. Patients who are known to be PML-RAR α -negative by the RT-PCR assay required in Section 5.1g below are not eligible. (NOTE: If the RT-PCR result is indeterminate, the central lab will request additional blood specimens to avoid indeterminate pretreatment results whenever possible; if the RT-PCR result remains indeterminate after the initial and any additional specimens are assayed, the patient will be eligible provided all other eligibility criteria are met. Patients may be registered before the RT-PCR assay result is known, but if the result is negative they must be removed from protocol treatment and treated at the physician's discretion; see Section 7.3d.)
3. Patients must have reached their 18th birthday.
4. Patients must not have prolonged QTc > 0.47 seconds.
5. Patients must not have received prior systemic chemotherapy for acute leukemia, with the exception of ATRA, which may be administered for up to 3 days prior to registration. Administration of hydroxyurea, corticosteroids, or leukapheresis to control high cell counts prior to registration is permitted.
6. Pretreatment cytogenetics must be performed on all patients. Participation in cytogenetic studies is mandatory. Collection of pretreatment specimens must be completed within 14 days prior to registration to S0535. Note that there are also additional time points at which specimens are required to be submitted for cytogenetics (see Section 15.2).
7. Pretreatment specimens for baseline RT-PCR assays for PML-RAR α must be collected and submitted within 14 days prior to registration to S0535. Note that there are also additional time points at which specimens are required to be submitted for RT-PCR assays (see Section 15.0). Specimens must be submitted to a CLIA approved lab.
8. Patients must not be pregnant or nursing because ATRA as well as other drugs used in this protocol may cause fetal harm and because of the potential for serious adverse reactions in nursing infants from the drug. Women of childbearing potential must have a negative pregnancy test performed within 14 days prior to registration. Women and men of reproductive potential must have agreed to use an effective contraceptive method.
9. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.
10. All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

Consolidation Therapy Registration:

After completing induction therapy, patients will be registered for consolidation treatment provided that they were eligible for the initial registration and satisfy the following additional criteria:

1. Patients must have achieved A1 marrow status, B1 peripheral blood status and C1 extramedullary disease status (see Section 10.1). Patients must have maintained a B1 peripheral blood status for at least 7 days prior to registration for this protocol step.
2. Specimens for RT-PCR assays for PML-RAR α must be collected and submitted within 8 weeks (preferably within 4 weeks) prior to this registration. Note that submission of specimens for RT-PCR assays is also required prior to Consolidation Cycle 3. Specimens must be submitted to a CLIA approved lab.

Maintenance Therapy Registration:

After completing consolidation therapy, patients will be registered for maintenance treatment provided that they were eligible for the consolidation registration and satisfy the following additional criterion:

1. Patients must remain in A1 marrow status, B1 peripheral blood status and C1 extramedullary disease status (see Section 10.1). Patients must have maintained a B1 peripheral blood status for at least 7 days prior to registration for this protocol step.
3. Specimens for RT-PCR assays for PML-RAR α must be collected and submitted within 8 weeks (preferably within 4 weeks) prior to this registration. Specimens must be submitted to a CLIA approved lab.

PRE-STUDY PARAMETERS

1. H&P, weight, height, BSA
2. CBC with differential
3. Chem including Mg, pregnancy test, cholesterol, triglycerides^a
4. PTT, PT, fibrinogen, FDP, D-dimer^a
5. Bone marrow biopsy/aspirate
6. Chest x-ray
7. EKG within 72 hours of day of treatment

^aThese test should be done in accordance with GMP

TREATMENT PLAN

INDUCTION CHEMOTHERAPY

<u>AGENT</u>	<u>DOSE</u>	<u>ROUTE</u>	<u>TIME</u>	<u>NOTES</u>
ATRA	45 mg/m ² /day (in 2 doses 22.5 mg/m ² every 12 hours)	PO	every 12 hrs, Day 1 to CR*	With food. See Section 7.3a
Gemtuzumab Ozogamicin [#]	9 mg/m ²	IV infusion over 2 hours	Day 1 only ^Ω	
Arsenic Trioxide	0.15 mg/kg/d	IV infusion over 2 hours	5 days/wk beginning on Day 10 and continuing until CR [^]	

* For maximum of 90 days, unless prohibited by either unacceptable toxicity or progressive disease.

^Ω G.O. may be delayed until Day 5 pending confirmation of APL diagnosis by FISH/cytogenetics, or RT-PCR. Hydroxyurea may be utilized during this time, up to 24 hours prior to initiation of gemtuzumab ozogamicin.

[^] For a maximum of 60 days, unless prohibited by either unacceptable toxicity or progressive disease.

[#] Recommended premedications prior to gemtuzumab: acetaminophen 1 gm orally, diphenhydramine 50 mg IV, and methylprednisolone 125 mg IV.

CONSOLIDATION CYCLES 1 AND 2

<u>AGENT</u>	<u>DOSE</u>	<u>ROUTE</u>	<u>TIME</u>	<u>NOTES</u>
Arsenic Trioxide	0.15 mg/kg/day	IV over 2 hours	5 days/week x 5 weeks	Repeat after 2 weeks rest*

* Consolidation Cycle 2 may be given after 2 weeks of rest following Cycle 1.

CONSOLIDATION CYCLES 3 AND 4

<u>AGENT</u>	<u>DOSE</u>	<u>ROUTE</u>	<u>TIME</u>	<u>NOTES</u>
ATRA	45 mg/m ² /day (in 2 doses, 22.5 mg/m ² every 12 hours)	PO	every 12 hours, Days 1-7	With food. See Section 7.5e
Daunomycin	50 mg/m ² /day	IV bolus or 1 hour infusion	Days 1-3	

CONSOLIDATION CYCLES 5 AND 6

<u>AGENT</u>	<u>DOSE</u>	<u>ROUTE</u>	<u>TIME</u>
Gemtuzumab Ozogamicin ^Ω	9 mg/m ²	IV infusion over 2 hours	Day 1

^Ω Recommended premedications prior to gemtuzumab: acetaminophen 1 gm orally, diphenhydramine 50 mg IV, and methylprednisolone 125 mg IV.

MAINTENANCE THERAPY

<u>AGENT</u>	<u>DOSE</u>	<u>ROUTE</u>	<u>TIME</u>	<u>NOTES</u>
ATRA	45 mg/m ² /day (in 2 doses 22.5 mg/m ² every 12 hours)	PO	Days 1-7 every 14 days	With food. See Section 7.7
6-MP	60 mg/m ² /d	PO	Daily	For 1 year
Methotrexate	20 mg/m ²	PO	Once/week	For 1 year.

See section 7 for specific instructions regarding ATRA dosing, ATRA syndrome, MUGA/Echo schedule, prolonged QTc and infection prophylaxis.

See section 8 for dose modifications.