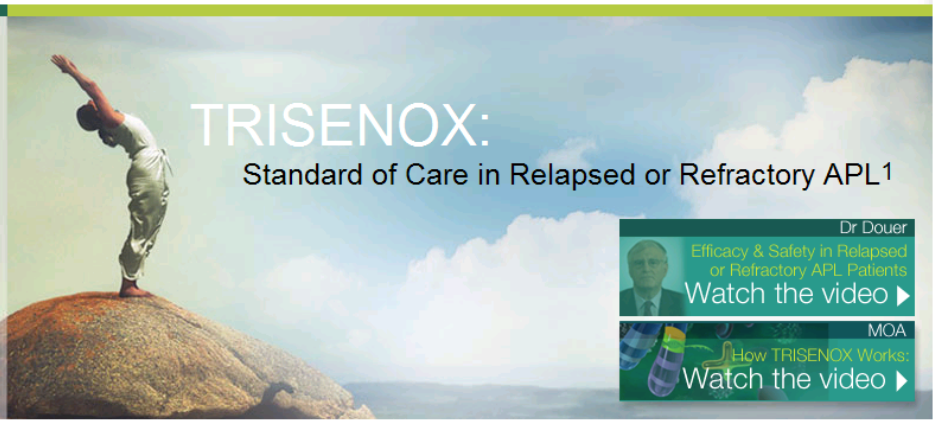

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APL Physicians' Network

Healthcare professionals exchanging information about their experiences on the treatment of relapsed or refractory APL.

AML vs APL

Take a compelling side-by-side look at acute myeloid leukemia (AML) and its most distinct subtype, acute promyelocytic leukemia (APL).

Downloadable Resources

Valuable resources for download including educational presentations and patient materials.

TRISENOX:

- Delivers high rates of complete remission in relapsed or refractory APL[2-4]
- Induces molecular remission in the majority of patients in relapse so chemotherapy may not be required[4]
- Was generally well tolerated in clinical trials, with manageable and reversible toxicities[4,5]
  - Low rate of grades 3 and 4 myelosuppression[2,5]
  - No alopecia[4,5]
  - Most common adverse events usually did not require interruption of TRISENOX® (arsenic trioxide) injection[5]
- Has multiple proposed mechanisms of action[4,6-10]
  - In APL, TRISENOX targets PML/RAR-alpha translocation
  - TRISENOX may target other leukemic pathways to induce apoptosis
- Offers a manageable dosing schedule that does not require premedication[5]

To report an adverse event, contact Cephalon Medical Services at 1-800-896-5855 or usmedinfo@cephalon.com.

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Serious adverse events, grade 3 or 4, were common. Those events attributable to TRISENOX in the phase 2 study of 40 patients with refractory or relapsed APL included QTc interval prolongation (n=16), APL differentiation syndrome (n=3), hyperleukocytosis (n=3), atrial dysrhythmias (n=2), hyperglycemia (n=2), and torsade de pointes (n=1).

In clinical trials, most patients taking TRISENOX experienced some drug-related toxicity, most commonly leukocytosis, gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), fatigue, edema, hyperglycemia, dyspnea, cough, rash or itching, headaches, and dizziness. These adverse effects have not been observed to be permanent or irreversible, nor do they usually require interruption of therapy.

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(unexplained fever, dyspnea and/or weight gain, abnormal chest auscultatory findings or radiographic abnormalities), high-dose steroids (dexamethasone 10 mg intravenously BID) should be immediately initiated, irrespective of the leukocyte count, and continued for at least 3 days or longer until signs and symptoms have abated. The majority of patients do not require termination of TRISENOX therapy during treatment of the APL differentiation syndrome.

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Cephalon Oncology

PHYSICIAN HOME
AML vs APL
ABOUT TRISENOX
EFFICACY & SAFETY
PRESCRIBING CONSIDERATIONS
RESOURCES

AML vs APL: Information for You and Your Patients

Acute promyelocytic leukemia (APL) is one of the most distinct subtypes of acute myeloid leukemia (AML).

TRISENOX® (arsenic trioxide) injection is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t (15;17) translocation or PML/RAR-alpha gene expression. This information is intended to elucidate the similarities and differences between APL and AML diseases.

PHYSICIAN NEEDS

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AML

Overview

Pre-treatment cytogenetic analysis shows an abnormal karyotype in nearly 60% of all AML patients. This diagnostic karyotype is a key determinant of outcome.[1]

- Average age is between 65 and 75 years[2]
- AML makes up nearly 25% of all leukemias in adults in the Western world[3]
- The mortality rate is higher in Caucasians than in African Americans[3]
- Nearly 8,950 Americans will die each year from AML[4]
- AML is the most common type of leukemia in adults and has the highest mortality rate of all leukemias[3]

Molecular Characteristics

The last 15 years have seen major advances in predicting the outcome of patients with newly diagnosed AML, and these have informed treatment approach.[1]

- The cytogenetic and molecular basis of AML helps provide a greater understanding of the biology of the subtypes of disease that predominate in different age groups. In addition, it provides major insights into the parameters underlying a number of long-established prognostic factors[1]:
  1. Age
  2. Presenting white blood cell (WBC) count
  3. Whether AML arises de novo or following an antecedent hematologic disorder or chemotherapy/radiation exposure

Risk of Relapse

Evidence suggests that using minimal residual disease (MRD) detection to direct the course of preemptive therapy helps provide the opportunity to improve the overall survival of patients with AML. The predictive value of MRD will help prevent the risk of relapse in those patients who would be likely to relapse without additional therapy.[1]

- Despite the substantial progress in the treatment of newly diagnosed AML, 20% to 40% of patients still do not achieve remission with standard induction chemotherapy[2]

Hematologic Characteristics

- Low numbers of healthy blood cells and high numbers of leukemia cells[5]
- Low numbers of white blood cells may lead to fever and frequent infections[5]
- Low red blood cell numbers may cause anemia, so symptoms could include feeling tired or weak, being short of breath, and looking pale[5]
- Platelets control bleeding. Low numbers can lead to easy bleeding or bruising and tiny red spots under the skin (petechiae)[5]
- Discomfort in bones or joints caused by the accumulation of leukemic cells in the bone marrow[4]

Treatment

Once AML is diagnosed, a course of treatment is usually started immediately.[5]

Because there is a range of treatment options 2 it's important to consult

APL

Overview

Acute promyelocytic leukemia is a distinct subtype of acute myeloid leukemia in which a balanced reciprocal translocation between chromosomes 15 and 17 results in the union of portions of the promyelocytic leukemia gene with the gene for retinoic acid receptor alpha.[6-8]

- Median age of those with APL is 40 years[9]
- APL makes up nearly 10% of all AML cases[8]
- Approximately 24% of Latino AML patients have APL[8]
- Approximately 10% to 20% die either before or during chemotherapy of bleeding attributable to disseminated intravascular coagulation, fibrinolysis, and proteolysis[7]
- APL can exist in 2 cell types: typical and microgranular[10]
- The life expectancy of an untreated APL patient is 3-4 months, but 70% to 90% of treated patients experience complete remission[4,11]

Molecular Characteristics

Through molecular surveillance, there is evidence that suggests preemptive therapy has benefits in patients with confirmed molecular relapse.[12]

- The genetic hallmark of APL is the reciprocal translocation of chromosomes 15 and 17 [t(15;17)], resulting in a fusion of the promyelocytic leukemia (PML) and retinoic acid receptor α (RAR-α) genes[13-15]
- The resulting all-*trans*-retinoic-acid (ATRA)–sensitive, PML/RAR-α fusion protein functions as an aberrant RAR receptor with altered DNA-binding properties and disrupts normal RAR-α and PML signaling[14,16]

Risk of Relapse

- Relapse still occurs in 10% to 30% of patients[17-20]
- When striving to help prevent the risk of relapse in patients with APL, platelet count cannot be ignored. This clinical presenting factor consistently correlates to the risk of relapse[21]
- Reverse transcriptase polymerase chain reaction (RT-PCR) allows physicians to detect molecular relapse early[14]

Hematologic Characteristics

- Low numbers of healthy blood cells and high numbers of leukemia cells[4]
- Low numbers of white blood cells may lead to fever, frequent infections, and swollen glands[4]
- Low red blood cell numbers may cause anemia; symptoms could include feeling tired or weak, being short of breath, and looking pale[4]
- Platelets control bleeding. Low numbers can lead to excessive bruising, bleeding, frequent or severe nosebleeds, bleeding from the gums, blood in the urine, and excessive bleeding during menstruation or after needle sticks for blood draws[4]

Treatment

The treatment of APL differs from that for all other forms of AML. In spite of the fact that APL is a subtype of AML, there are different treatments available for APL patients that offer high remission rates.[4]

Because there is a range of treatment options,* it's important to consult with an AML expert.

treatments available for APL patients that offer high remission rates.* Contact an expert in the treatment of APL via the APL Physicians' Network.

More information on treatment options.

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Cephalon Oncology

About TRISENOX

Successful Therapy for Relapsed or Refractory APL

Experience the "History of Arsenic Trioxide."

Successful Therapy for Relapsed or Refractory APL

Clinical studies have demonstrated:

The important role arsenic trioxide may have in the treatment of patients with relapsed or refractory acute promyelocytic leukemia (APL). When initial therapies fail, TRISENOX® (arsenic trioxide) injection has shown to be a successful second-line therapy.

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Current First-line Therapy for APL

In the past, APL was associated with a high risk of early mortality, but with the introduction of all-*trans* retinoic acid (ATRA), APL has become the most curable subtype of acute myeloid leukemia (AML).[1,2]

Multiple studies have established that the combination of ATRA and chemotherapy in newly diagnosed patients has increased the cure rate from 35% to 70% in patients treated with chemotherapy alone.[2]

The incorporation of ATRA into the treatment regimen has more than doubled the survival rate of newly diagnosed patients over that achieved with chemotherapy alone.[2-7] Given this success, the current first-line standard treatment given to patients with newly diagnosed APL consists of ATRA and anthracycline-based cytotoxic chemotherapy.[8]

Daunorubicin and idarubicin are two commonly used anthracyclines shown to induce complete remission in 60% to 80% of APL patients.[9-11]

Relapse and Resistance

Despite improvements in remission and survival rates, 20% to 30% of patients relapse and are often resistant to further treatment with ATRA.[1,2,8]

Approximately 50% of the patients in first relapse presently have the chance to achieve long-lasting second remissions and probably cure with salvage regimens.[1] Salvage therapy often involves high doses of cytotoxic chemotherapy, followed by either autologous or allogeneic transplantation. With this approach, these patients are exposed to, and some patients may die from, the toxic effects of chemotherapy, an important consideration in treating young or elderly patients. TRISENOX may fill the critical need for therapeutic options in treating relapsed or refractory APL.[3]

The Role of Arsenic Trioxide

Studies of arsenic trioxide have demonstrated a high rate of complete remission, suggesting that TRISENOX is an important treatment option for patients who have relapsed from, or did not respond to, initial therapy.[3,12] According to the National Comprehensive Cancer Network (NCCN) guidelines for oncology, arsenic trioxide is the standard of care for patients who have relapsed from, or did not respond to, their initial treatment.[13]

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Prior to initiating therapy with TRISENOX, a 12-lead ECG should be performed and serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed; pre-existing electrolyte abnormalities should be corrected and, if possible, drugs that are known to prolong the QT interval should be discontinued. For QTc greater than 500 msec, corrective measures should be completed and the QTc reassessed with serial ECGs prior to considering using TRISENOX. During therapy with TRISENOX, potassium concentrations should be kept above 4 mEq/L and magnesium concentrations should be kept above 1.8 mg/dL. Patients who reach an absolute QT interval value > 500 msec should be reassessed and immediate action should be taken to correct concomitant risk factors, if any, while the risk/benefit of continuing versus suspending TRISENOX therapy should be considered. If syncope, rapid or irregular heartbeat develops, the patient should be hospitalized for monitoring, serum electrolytes should be assessed, TRISENOX therapy should be temporarily discontinued until the QTc interval regresses to below 460 msec, electrolyte abnormalities are corrected, and the syncope and irregular heartbeat cease. There are no data on the effect of TRISENOX on the QTc interval during the infusion.

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Efficacy and Safety

The Clinical Studies and Trials

Efficacy and Safety

TRISENOX® (arsenic trioxide) injection fulfills an unmet medical need based on its ability to induce complete remission in patients with relapsed or refractory acute promyelocytic leukemia (APL) as demonstrated in clinical studies. TRISENOX delivered both high rates of remission and survival in this type of leukemia, giving hope to APL patients who have relapsed or who did not respond to their initial therapy. Based on these data, TRISENOX was approved by the FDA, and the National Comprehensive Cancer Network (NCCN) guidelines currently recommend arsenic trioxide therapy as the standard of care for patients with relapsed or refractory APL.[1,2]

PHYSICIAN NEEDS

Request contact from a sales rep or Medical Science Liaison (MSL), or request medical, reimbursement, or clinical trials information.

In clinical studies, TRISENOX was generally well tolerated with manageable and reversible toxicities. TRISENOX works with minimal chemotherapy-related side effects.

To report an adverse event, contact Cephalon Medical Services at 1-800-896-5855 or usmedinfo@cephalon.com.

References:

1. TRISENOX® (arsenic trioxide) Injection [current approved prescribing information]. Frazer, PA: Cephalon, Inc.
2. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia — v.2.2011. http://www.nccn.org/professionals/physician_gls/PDF/aml.pdf

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TRISENOX is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.

Serious adverse events, grade 3 or 4, were common. Those events attributable to TRISENOX in the phase 2 study of 40 patients with refractory or relapsed APL included QTc interval prolongation (n=16), APL differentiation syndrome (n=3), hyperleukocytosis (n=3), atrial dysrhythmias (n=2), hyperglycemia (n=2), and torsade de pointes (n=1).

In clinical trials, most patients taking TRISENOX experienced some drug-related toxicity, most commonly leukocytosis, gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), fatigue, edema, hyperglycemia, dyspnea, cough, rash or itching, headaches, and dizziness. These adverse effects have not been observed to be permanent or irreversible, nor do they usually require interruption of therapy.

In a pediatric clinical trial of 13 patients (ages 4-20), additional drug-related toxicities included: gastrointestinal disorders, metabolic disorders, respiratory disorders, cardiac failure congestive, neuralgia, and enuresis. One case each of pulmonary edema and caecitis were considered serious reactions.

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Efficacy Information for TRISENOX

Demonstrated Efficacy of TRISENOX

Demonstrated Efficacy

In clinical studies, TRISENOX® (arsenic trioxide) injection has shown both high rates of remission (complete and molecular) and high rates of survival for patients with relapsed or refractory acute promyelocytic leukemia (APL).[1]

Remission

TRISENOX induced a high rate of molecular remission (MR)* in patients who achieved complete remission (CR).[1]

*Defined as the absence of PML/RAR-alpha transcript.[1]

PHYSICIAN NEEDS

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US Multicenter Trial/Prescribing Information[2]

70% (28/40) Complete remission†

79% (22/28) Molecular remission‡

† Complete remission, as defined in the Prescribing Information: Absence of visible leukemic cells in bone marrow and peripheral recovery of platelets and white blood cells with a confirmatory bone marrow ≥ 30 days later.[2]

‡ In patients who met the criteria for complete remission, molecular remission monitored by reverse transcriptase-polymerase chain reaction to detect PML/RAR-alpha transcripts.[2]

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Published Results

Published remission rate data below have been adjusted based on the revised definition of remission.[3]§

§ The definition was revised by the International Working Group of investigators in Madrid, Spain, 2001. The definition given in the Prescribing Information, which requires a confirmatory bone marrow, is no longer current.[3]

Published US Multicenter Trial[1]

85% (34/40) Complete remission

86% (25/29)‖ Molecular remission

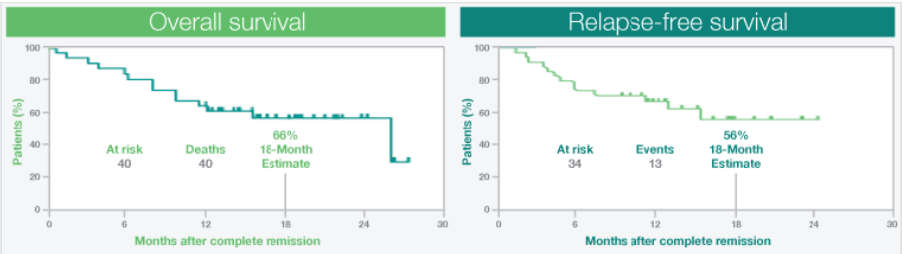
The US multicenter trial was an open-label, single-arm, noncomparative trial in 40 patients with APL who had either relapsed from or did not respond to induction chemotherapy using anthracycline and at least one course of ATRA or 9-cis retinoic acid. Patients could receive up to 60 doses of TRISENOX 0.15 mg/kg/day. Twenty-four patients were female; 35 were ≥18 years of age; 21 patients had 1 relapse; and 19 patients had >1 relapse.

‖Of those patients who achieved CR.

Survival

Over half the patients in the US multicenter trial were alive at the 18-month follow-up, irrespective of the number of prior therapies and/or relapses.[1]

Survival estimates for relapsed or refractory APL patients treated with TRISENOX[1]:



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References:

1. Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol*. 2001;19:3852-3860.
2. TRISENOX® (arsenic trioxide) Injection [current approved prescribing information]. Frazer, PA: Cephalon, Inc.
3. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *J Clin Oncol*. 2003;21:4642-4649.

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Safety Profile for TRISENOX

Discover Safety Profiles for Your TRISENOX

Proven Safety Profile

The safety of TRISENOX® (arsenic trioxide) injection has been demonstrated in clinical trials:

- TRISENOX was generally well tolerated with manageable and reversible toxicities[1,2]
- TRISENOX exhibited low rates of grades 3 and 4 myelosuppression[1,3]
- There was no incidence of alopecia[1,2]
- Most common adverse events usually did not require interruption of TRISENOX[1]

PHYSICIAN NEEDS

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QT Interval Prolongation and ECG Abnormalities

- QT prolongation is an expected but manageable event[4]
- QT prolongation is reversible[4]
- Sixteen of 40 patients had at least 1 on-study ECG that showed QTc prolongation[3]
- Two of 40 patients had atrial dysrhythmias[1]
- For management of QT abnormalities, please see recommendations as noted in the BOXED WARNING

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APL Differentiation Syndrome — Effectively Treated With Dexamethasone

- Ten of 40 patients developed symptoms suggestive of APL differentiation syndrome (3 were serious)[1,3]
  - All 10 patients had leukocytosis and received dexamethasone (10 mg BID IV for ≥3 days)[3]
  - Eight patients required a brief therapy interruption (1 to 5 days)[3]
  - All 10 patients achieved complete remission[3]
- The management of the syndrome has not been fully studied, but high-dose steroids have been used to mitigate signs and symptoms
- Termination of TRISENOX was not required in the majority of patients[1]; interruption of therapy is necessary if symptoms of APL syndrome do not respond to steroid treatment

MOA

How TRISENOX Works:
Watch the video

Hyperleukocytosis — Resolved With Continuation of TRISENOX

- Of 20 patients who developed leukocytosis, 1 was severe (grade 3 or 4)[1]
- With the continuation of therapy with TRISENOX, leukocytosis resolved a median 10.5 days after peak WBC count (range: 3 to 27 days)[3]
- Hyperleukocytosis was not treated with additional chemotherapy[1]

Other Events Typical of Chemotherapy

- Neuropathy symptoms were mild, grade 1 in the majority[3]
- No significant hepatotoxicity was observed in the multicenter trial[3]

Drug Interactions

- No formal assessments of pharmacokinetic drug-drug interactions between TRISENOX and other drugs have been conducted. The methyltransferases responsible for metabolizing arsenic trioxide are not members of the cytochrome P450 family of isoenzymes (see PRECAUTIONS in the full Prescribing Information)[1]
- Caution is advised when TRISENOX is coadministered with other medications that can prolong the QT interval (eg, certain antiarrhythmics or thioridazine) or lead to electrolyte abnormalities (such as diuretics or amphotericin B)[1]

TRISENOX is contraindicated in patients who are hypersensitive to arsenic.[1]

Click here to find out more about the medicinal role of arsenic.

To report an adverse event, contact Cephalon Medical Services at 1-800-896-5855 or usmedinfo@cephalon.com.

References:

1. TRISENOX® (arsenic trioxide) Injection [current approved prescribing information]. Frazer, PA: Cephalon, Inc.
2. Douer D, Tallman MS. Arsenic trioxide: new clinical experience with an old medication in hematologic malignancies. *J Clin Oncol*. 2005;23:2396-2410.
3. Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol*. 2001;19:3852-3860.
4. Barbey JT, Pezzullo JC, Soignet SL. Effect of arsenic trioxide on QT interval in patients with advanced malignancies. *J Clin Oncol*. 2003;21:3609-3615.

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Adverse events (AEs) in the multicenter trial

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See the drop-down arrow to the right of each heading below for a full list of adverse events.

Adverse events (any grade) occurring in ≥5% of 40 patients with APL who received TRISENOX (arsenic trioxide) injection at a dose of 0.15 mg/kg/day.

System organ class

General disorders and administration site conditions

	All adverse events, any grade		Grade 3 & 4 events	
Adverse event	n	%	n	%
Fatigue	25	63	2	5
Pyrexia (fever)	25	63	2	5
Edema — non-specific	16	40		
Rigors	15	38		
Chest pain	10	25	2	5
Injection site pain	8	20		
Pain — non-specific	6	15	1	3
Injection site erythema	5	13		
Injection site edema	4	10		
Weakness	4	10	2	5
Hemorrhage	3	8		
Weight gain	5	13		
Weight loss	3	8		
Drug hypersensitivity	2	5	1	3

Gastrointestinal disorders

Metabolism and nutrition disorders

Nervous system disorders

Respiratory

Skin and subcutaneous tissue disorders

Cardiac disorders

Metabolism and nutrition disorders
Nervous system disorders
Respiratory
Skin and subcutaneous tissue disorders

Cardiac disorders

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Infections and infestations

Musculoskeletal, connective tissue, and bone disorders

Infections and infestations

Musculoskeletal, connective tissue, and bone disorders

Hematologic disorders

Vascular disorders

Psychiatric disorders

Ocular disorders

Psychiatric disorders

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Renal and urinary disorders

Reproductive system disorders

Ear disorders

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Patient Management Essential for Success

Initiating TRISENOX Therapy for Your Relapsed or Refractory APL Patients

If patients have not achieved remission following first-line therapy for acute promyelocytic leukemia (APL), TRISENOX® (arsenic trioxide) injection has proven to be an important second-line treatment option. Prescribing TRISENOX can give new hope to your relapsed or refractory APL patients.

Studies have demonstrated the role of reverse transcriptase-polymerase chain reaction (RT-PCR) testing throughout treatment in the assessment of disease progression and the evaluation of therapy management.[1-4] In this section you will learn more about RT-PCR testing and how it relates to treatment of your APL patients.

PHYSICIAN NEEDS

Request contact from a sales rep or Medical Science Liaison (MSL), or request medical, reimbursement, or clinical trials information.

Proper patient management is essential for success with TRISENOX therapy, including monitoring for differentiation syndrome, electrolyte imbalances, blood chemistry abnormalities, QT prolongation, hyperleukocytosis, rash, and other potential side effects.

TRISENOX offers manageable treatment schedules for you and your patients. Therapy with TRISENOX does not require premedication, and TRISENOX can be administered in an outpatient setting. It is given intravenously, usually over 1 to 2 hours.

To report an adverse event, contact Cephalon Medical Services at 1-800-896-5855 or usmedinfo@cephalon.com.

References:

1. Lowenberg B, Griffin JD, Tallman MS. Acute myeloid leukemia and acute promyelocytic leukemia. *Hematology Am Soc Hematol Educ Program*. 2003;82-101.
2. Diverio D, Rossi V, Avvisati G, et al. Early detection of relapse by prospective reverse transcriptase-polymerase chain reaction analysis of the PML/RAR alpha fusion gene in patients with acute promyelocytic leukemia enrolled in the GIMEMA-AIEOP multicenter "AIDA" trial. GIMEMA-AIEOP Multicenter "AIDA" Trial. *Blood*. 1998;92:784-789.
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TRISENOX is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.

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In clinical trials, most patients taking TRISENOX experienced some drug-related toxicity, most commonly leukocytosis, gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), fatigue, edema, hyperglycemia, dyspnea, cough, rash or itching, headaches, and dizziness. These adverse effects have not been observed to be permanent or irreversible, nor do they usually require interruption of therapy.

In a pediatric clinical trial of 13 patients (ages 4-20), additional drug-related toxicities included: gastrointestinal disorders, metabolic disorders, respiratory disorders, cardiac failure congestive, neuralgia, and enuresis. One case each of pulmonary edema and caecitis were considered serious reactions.

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Treating Patients With TRISENOX

Finding the Right Patient

Selecting Patients for TRISENOX Therapy

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The first consideration for patient selection is determining where your patient is in the APL treatment sequence. If your APL patient has relapsed after initial therapy, or if he/she did not respond to initial therapy, TRISENOX may be an appropriate option. TRISENOX provides the opportunity for complete remission and high rates of survival in patients with refractory/relapsed APL.[1]
According to the National Comprehensive Cancer Network (NCCN) guidelines for oncology, arsenic trioxide is the standard of care for relapsed or refractory APL patients.[2]

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1. Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol*. 2001;19:3852-3860.
2. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia — v.2.2011. http://www.nccn.org/professionals/physician_gls/PDF/aml.pdf

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Selecting Patients for TRISENOX Therapy

Manageable Monitoring Profile

Proactive monitoring is essential to proper management of TRISENOX® (arsenic trioxide) injection therapy.

APL differentiation syndrome: Signs are subtle and easy to overlook[1]

- Weigh patient daily to detect weight changes
- Instruct patient to immediately report fever, sudden weight gain (> 2 lbs in 24 hours), musculoskeletal pain, fluid retention, and/or dyspnea
- At first signs of syndrome, administer dexamethasone 10 mg IV BID for a minimum of 3 days or longer until signs and symptoms have abated
- In clinical trials, termination of TRISENOX was not required in the majority of patients[1]; interruption of therapy is necessary if symptoms of APL syndrome do not respond to steroid treatment
- Treat weight gain symptomatic of fluid overload (in absence of differentiation syndrome) with potassium-sparing diuretics

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Electrolytes: Monitor throughout treatment[1]

- Induction: at least twice weekly, and more frequently for clinically unstable patients[1]
- Consolidation: at least weekly[1]
- Assess serum electrolytes (potassium, magnesium, calcium) and creatinine; preexisting electrolyte abnormalities should be corrected
- Supplement electrolytes as needed
  - Maintain serum potassium > 4.0 mEq/L
  - Maintain serum magnesium > 1.8 mg/dL

If rash occurs[1]:

- Interruption of therapy with TRISENOX may not be necessary[1]
- Topical steroids may be effective; use topical antihistamines for pruritus[1]

Blood chemistries: Monitor twice weekly during induction and weekly during consolidation

- TRISENOX may increase blood sugar levels[1]
- Exercise caution in patients with renal and hepatic impairment. Please refer to Prescribing Information[1]
- Transient increases in transaminase levels may occur. These events typically do not require dose reduction or interruption of therapy

Monitor 12-lead ECGs at baseline, then weekly[1]

- Monitor more frequently in patients at risk for a cardiac event or if QT increases
- Avoid concomitant drugs that prolong QT interval; check online at www.azcert.org/medical-pros/drug-lists/drug-lists.cfm
- If absolute QT is > 500 msec, immediately correct risk factors, such as electrolytes and concomitant drugs
  - If syncope, or rapid or irregular heartbeat occurs, hospitalize and monitor continuously; assess and correct electrolytes. Hold TRISENOX until QTc is < 460 msec and symptoms resolve
  - Hyperleukocytosis[1]
- Usually self-limiting
- Additional chemotherapy may not be required
- Interruption of therapy with TRISENOX may not be necessary

Click here to review the safety profile for TRISENOX.

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References:

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RT-PCR Testing

RT-PCR Testing for TRISENOX

Tracking APL Progress With RT-PCR Testing

Testing disease status helps to predict relapse and potentially improve outcomes for acute promyelocytic leukemia (APL) patients.[1-4]

One method of assessing APL status is reverse transcriptase-polymerase chain reaction testing, or RT-PCR testing. RT-PCR testing presents the opportunity to detect impending relapse rather than wait for signs of clinical relapse. Based on a review of the literature, Tallman and colleagues concluded that a reasonable schedule of testing is to obtain at least 2 successive marrow samples at the end of treatment performed every 3 months for the first 2 years of CR, and then every 6 months for the next 2 to 3 years.[1]

PHYSICIAN NEEDS

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Genetic testing can help track disease status, predict relapse, and improve outcomes.

RT-PCR testing analyzes the chromosome abnormalities that define APL specifically. APL is usually marked by a translocation of genes between chromosomes 15 and 17, represented as t(15;17).[5-8] Part of the promyelocytic leukemia PML gene transfers to chromosome 17 and part of the RAR-alpha (retinoic acid receptor-alpha) gene transfers to chromosome 15. The result is a fusion protein product with characteristics of both the PML gene and the RAR-alpha receptor protein.[5-8]

Expression of the fusion produced by the translocation of genes between chromosomes 15 and 17 is detected with the RT-PCR test, which offers the following 2 benefits.

1. The test is predictive of relapse and survival.
A positive PML/RAR-alpha test after consolidation therapy reliably predicts subsequent hematologic relapse, whereas repeatedly negative results are associated with long-term survival in the majority of patients.[1] In one study, 163 newly diagnosed APL patients were induced into remission by ATRA combined with chemotherapy, and were tested at regular intervals after the end of treatment. Twenty of the 21 patients who converted to a positive PCR relapsed within a median of 3 months, whereas the 3-year estimate of relapse risk of patients who tested negative at least twice after consolidation was less than 10%.[1,2]

2. Test results can guide therapy, leading to improved patient outcomes.
Patients who convert to a positive PCR can be salvaged early with chemotherapy prior to overt disease.[1,3] This results in a significantly improved outcome compared to delaying treatment until morphologic evidence of relapse. It is anticipated that therapy at the time of molecular relapse will be associated with a lower mortality rate than that observed with reinduction of overt disease.[1,3] In one study, 14 APL patients were prospectively monitored after consolidation therapy with the AIDA protocol (all-*trans* retinoic acid [ATRA] plus idarubicin). Patients were treated at the time of molecular relapse (defined as 2 successive RT-PCR positive samples), rather than at clinical relapse. Early treatment for relapse with 30 days of oral ATRA followed by 4 daily courses of chemotherapy with cytarabine and mitoxantrone resulted in achievement of a second molecular remission in 12 patients (86%).[3]

Click here to review how TRISENOX may work to achieve remission for your relapsed or refractory APL patients.

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6. Douer D, Tallman MS. Arsenic trioxide: new clinical experience with an old medication in hematologic malignancies. *J Clin Oncol*. 2005;23:2396-2410.
7. Miller WH Jr, Schipper HM, Lee JS, et al. Mechanisms of action of arsenic trioxide. *Cancer Res*. 2002;62:3893-3903.
8. Davison K, Mann KK, Miller WH Jr. Arsenic trioxide: mechanisms of action. *Semin Hematol*. 2002;39(suppl 1):3-7.

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Dosing and Administration

Dosing and Administration for TRISENOX

Manageable Dosing, Sensitive to Patient Needs

TRISENOX® (arsenic trioxide) injection offers manageable administration schedules for patients and healthcare providers:

- TRISENOX does not require premedication[1]
- TRISENOX can be administered in an outpatient setting[1]
- TRISENOX is administered intravenously[1]

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Recommended treatment schedule

Induction Treatment With TRISENOX:

- **In a multicenter study, the median time to bone marrow remission (BMR) in relapsed or refractory patients treated with TRISENOX was 44 days; median time to onset of CR was 53 days[1]**
- Total induction treatment with TRISENOX can consist of up to 60 doses,[1] offering flexibility in treatment to CR and MR
- Administer TRISENOX intravenously at a dose of 0.15 mg/kg daily until BMR (total induction dose should not exceed 60 doses)[1]
- To achieve optimal clinical benefits, complete appropriate induction dosing regimen[2]

Consolidation Treatment With TRISENOX:

- **Complete appropriate consolidation dosing regimen to obtain optimal clinical benefits[2]**
- Administer TRISENOX intravenously at a dose of 0.15 mg/kg daily for 25 doses over a period of up to 5 weeks[1]
- Begin TRISENOX treatment 3 to 6 weeks after completion of induction therapy[1]
- In a multicenter trial, 86% of patients who achieved CR converted to negative for the presence of PML/RAR-alpha transcript after induction (n=14) or subsequent consolidation (n=11)[2]
  - Based on revised International Working Group criteria (79% based on Prescribing Information definition)

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2. Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol*. 2001;19:3852-3860.

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In a pediatric clinical trial of 13 patients (ages 4-20), additional drug-related toxicities included: gastrointestinal disorders, metabolic disorders, respiratory disorders, cardiac failure congestive, neuralgia, and enuresis. One case each of pulmonary edema and caecitis were considered serious reactions.

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Oncology

Trisenox (arsenic trioxide) injection

TO REPORT SIDE EFFECTS: 1-800-896-5855 or usmedinfo@cephalon.com [Send to a Colleague]

The APL Physicians' Network

Search by region or specialty to quickly locate the assistance you need to answer immediate questions or concerns about treating patients.

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gershwin blyden	Southeast	FL	3057570113	gershwb@aol.com	1-5
Guillermo Garcia-Manero	Central	TX	713-792-7305	ggarciam@mdanderson.org	> 10
Heiko Becker	Midwest	OH		heiko.becker@osumc.edu	1-5
Jose Cervantes	Northeast	NY	718 835 1056	joecervmd@gmail.com	1-5
Marin Xavier	West	CA	619-713-7900	marinfeldman@hotmail.com	1-5

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Resources Overview

Efficacy and Safety in Patients With Relapsed or Refractory Acute Promyelocytic Leukemia

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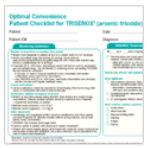
APL Physicians' Network

Contribute to this community of healthcare professionals dedicated to the exchange of information about their experiences on the treatment of relapsed or refractory APL.

APL Physicians' Network »



Patient Checklist

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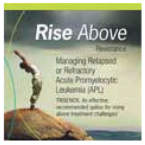

Managing Relapsed or Refractory Acute Promyelocytic Leukemia (APL)

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Your Goal: Molecular Remission

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How TRISENOX Works: Watch the video

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Cephalon Oncology

Monitoring to detect minimal residual disease or molecular relapse is the strongest predictor for clinical relapse and relapse-free survival[6]

- **Patients who achieve molecular remission have a better prognosis[7]**
- **TRISENOX delivers overall and relapse-free survival in relapsed or refractory APL[2]**

Important Safety Information

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Please see accompanying Prescribing Information, including BOXED WARNING.

References: 1. Diverio D, Rossi V, Avvisati G, et al. Early detection of relapse by prospective reverse transcriptase-polymerase chain reaction analysis of the PML/RARα fusion gene in patients with acute promyelocytic leukemia enrolled in the GIMEMA-AIEOP multicenter "AIDA" trial. *Blood.* 1998;92:784-789. **2.** Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol.* 2001;19:3852-3860. **3.** TRISENOX® (arsenic trioxide) injection [current approved prescribing information]. Cephalon, Inc. **4.** Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *J Clin Oncol.* 2003;21:4642-4649. **5.** NCCN Clinical Practice Guidelines in Oncology™: Acute Myeloid Leukemia—V.1.2011. National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/PDF/aml.pdf. Accessed August 19, 2010. **6.** Grimwade D, Jovanovic JV, Hills RK, et al. Prospective minimal residual disease monitoring to predict relapse of acute promyelocytic leukemia and to direct pre-emptive arsenic trioxide therapy. *J Clin Oncol.* 2009;27:3650-3658. **7.** Douer D. Acute promyelocytic leukemia: a target for preemptive strike? *Blood.* 2004;104:1913-1914

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TRI-2003 August 2010 Printed in USA.

Trisenox® (arsenic trioxide) injection

www.TRISENOX.com

FPO

In relapsed or refractory acute promyelocytic leukemia (APL)

Your Goal: Molecular Remission

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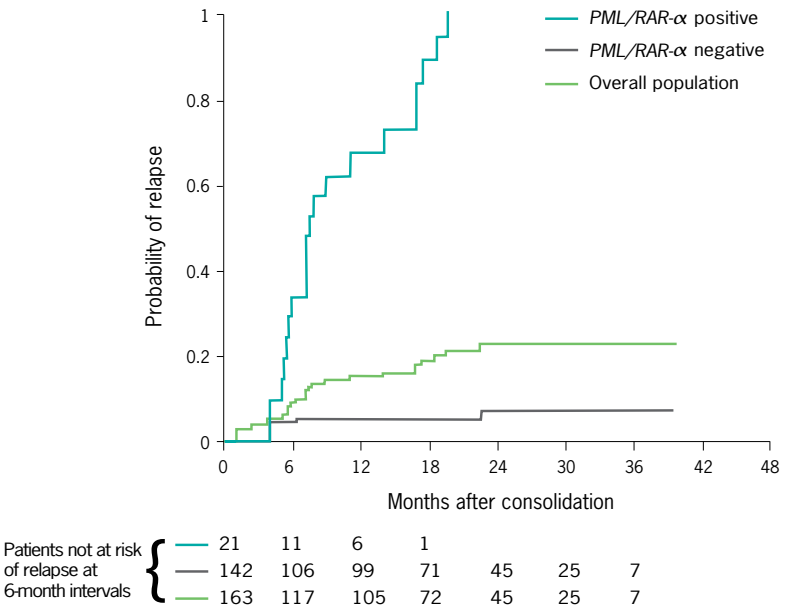
Trisenox® (arsenic trioxide) injection

PML/RAR-α* RT-PCR† POSITIVITY PREDICTS RELAPSE IN APL

Estimates of relapse risk based on RT-PCR testing for *PML/RAR-α*[1‡]



Adapted from Diverio D et al. *Blood*. 1998;92:784-789.[1]
*Promyelocytic leukemia/retinoic acid receptor alpha.
† Reverse transcriptase–polymerase chain reaction.
‡ Kaplan-Meier estimates of the relapse risk according to PCR analysis of *PML/RAR-α*.

STUDY DESIGN[1]

- Prospective RT-PCR analyses were performed from 1993–1997 at diagnosis and during follow-up on bone marrow samples of 163 patients with newly diagnosed *PML/RAR-α*-positive APL enrolled in the GIMEMA AIDA trial
- Treatment consisted of all-*trans* retinoic acid (ATRA) + idarubicin for induction, followed by 3 polychemotherapy consolidation courses
- RT PCR assay sensitivity for *PML/RAR-α* was 10^{-4}

- Twenty-one of the 163 patients tested PCR-positive at least once during follow-up. Of these 21 patients, 95% underwent hematologic relapse within a median of 3 months (range 1-14 months) from the first PCR test[1]
  — 81% of these conversions were within 6 months of postconsolidation[1]

CHOOSE TRISENOX® (ARSENIC TRIOXIDE) INJECTION TO DELIVER MOLECULAR REMISSION AFTER RELAPSE

Single-agent TRISENOX achieves molecular remission in relapsed or refractory APL[2,3]

US Multicenter Trial/Prescribing Information[3]

79% (22/28) Molecular remission[§‖]

Published US Multicenter Trial[2]

Published remission rate data below have been adjusted based on the revised definition of molecular.[4¶]

86% (25/29)[#] Molecular remission

Please see NCCN Guidelines for instructions on testing for molecular remission and relapse using RT-PCR.[5]

§ Complete remission, as defined in the Prescribing Information: absence of visible leukemic cells in bone marrow and peripheral recovery of platelets and white blood cells with a confirmatory bone marrow 30 days later.[3]
‖ In patients who met the criteria for complete remission, molecular remission was monitored by reverse transcriptase–polymerase chain reaction to detect *PML/RAR-α* transcripts.[3]

¶ The definition was revised by the International Working Group of investigators in Madrid, Spain, 2001. The definition given in the prescribing information, which requires a confirmatory bone marrow biopsy, is no longer current.[4]
# Of those patients who achieved complete response and had assessable assays (n=29/40).[2]

STUDY DESIGN[2]

- A US multicenter, open-label, single-arm, noncomparative trial in 40 patients with APL who had either relapsed from, or did not respond to, induction chemotherapy using an anthracycline and at least 1 course of ATRA or 9-*cis* retinoic acid
- Patients could receive TRISENOX 0.15 mg/kg/day, up to 60 doses during induction
- Twenty-four patients were female; 35 were ≥18 years of age; 21 patients had 1 relapse; and 19 patients had >1 relapse

Normalization of coagulopathy[2]

- At the time of study enrollment, 83% of patients (n=40) had evidence of coagulopathy: 48% clinical, 35% subclinical
- Following the initiation of TRISENOX, coagulopathy resolved over a median of 11 days (range 4 to 28)

TRISENOX allows you to achieve your goal of molecular remission in patients with relapsed or refractory APL[2,3]

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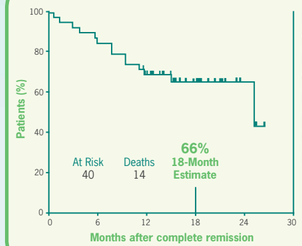
Rise above resistance by staying the course with TRISENOX

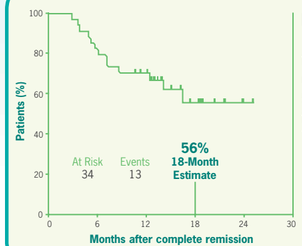
A multicenter study demonstrated that, when treating patients with relapsed or refractory APL, completing the full 5-week consolidation course of therapy with TRISENOX helped patients achieve overall and relapse-free survival.[3]

Overall Survival[3]



More than half of the patients in a multicenter study were alive at 18 months, irrespective of the number of prior therapies and/or relapses[3]

Relapse-Free Survival[3]



Kaplan-Meier 18-month relapse-free survival estimate was 56% in patients treated with TRISENOX[3]

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Recognizing Initial Treatment Failure in APL

Second-line treatment options do exist for relapsed or nonresponding patients[1]

Any failure of first-line treatment to achieve complete, long-lasting remission warrants changing to a second-line therapy.[1] NCCN Guidelines recommend arsenic trioxide for those patients who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy.[1]

Complete Remission Criteria Checklist[1,4]

To qualify as complete remission (CR) all of the following *must be met and maintained*[1,4]:

- Patient achieves a morphologic leukemia-free state
  - Bone marrow <5% blasts in an aspirate with spicules
  - No detectable blasts with Auer rods or persistence of extramedullary disease

  AND
  - Absolute neutrophil count >1000/μL
  - Platelets ≥100,000/μL
  - No residual evidence of extramedullary disease
  - Morphologic CR—patient independent of transfusions
  - Cytogenetic CR—cytogenetics normal (in those with previously abnormal cytogenetics)
  - Molecular CR—molecular studies negative*
- Patients failing to achieve a complete response are considered treatment failures[1]

*Clinically relevant only in APL and Ph+ leukemia.

Rise Above Resistance

- **Think APL first—identifying APL in the AML population can make all the difference**
- Relapsed or refractory APL is a medical emergency[2]
- Molecular testing can quickly and definitively diagnose APL[1]
- **Arsenic trioxide is the standard of care in relapsed or refractory APL**[1]
- TRISENOX induced a high rate of MR in those patients who achieved CR[3]
- TRISENOX demonstrated overall and relapse-free survival in relapsed or refractory APL patients[3]
- Optimal benefits are achieved when a full 5-week consolidation course of therapy is administered[3]
  - Median time to bone marrow remission in patients treated with TRISENOX was 44 days[5]
  - Median time to onset of CR was 53 days[5]

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References: 1. NCCN Clinical Practice Guidelines in Oncology™: Acute Myeloid Leukemia—V.2.2010. National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/PDF/aml.pdf. Accessed February 10, 2010. **2.** Lo-Coco F, Ammatuna E. The biology of acute promyelocytic leukemia and its impact on diagnosis and treatment. *Hematology Am Soc Hematol Educ Program.* 2006:156-161. **3.** Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol.* 2001;19:3852-3860. **4.** Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *J Clin Oncol.* 2003;21:4642-4649. **5.** TRISENOX® (arsenic trioxide) injection [current approved prescribing information]. Frazer, PA: Cephalon, Inc.

Cephalon® Oncology

Trisenox® (arsenic trioxide) injection

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Rise Above Resistance

Managing Relapsed or Refractory Acute Promyelocytic Leukemia (APL)

TRISENOX: An effective, recommended option for rising above treatment challenges[1]

TRISENOX (arsenic trioxide) is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.

Refer to BOXED WARNING and accompanying full Prescribing Information.

Trisenox® (arsenic trioxide) injection

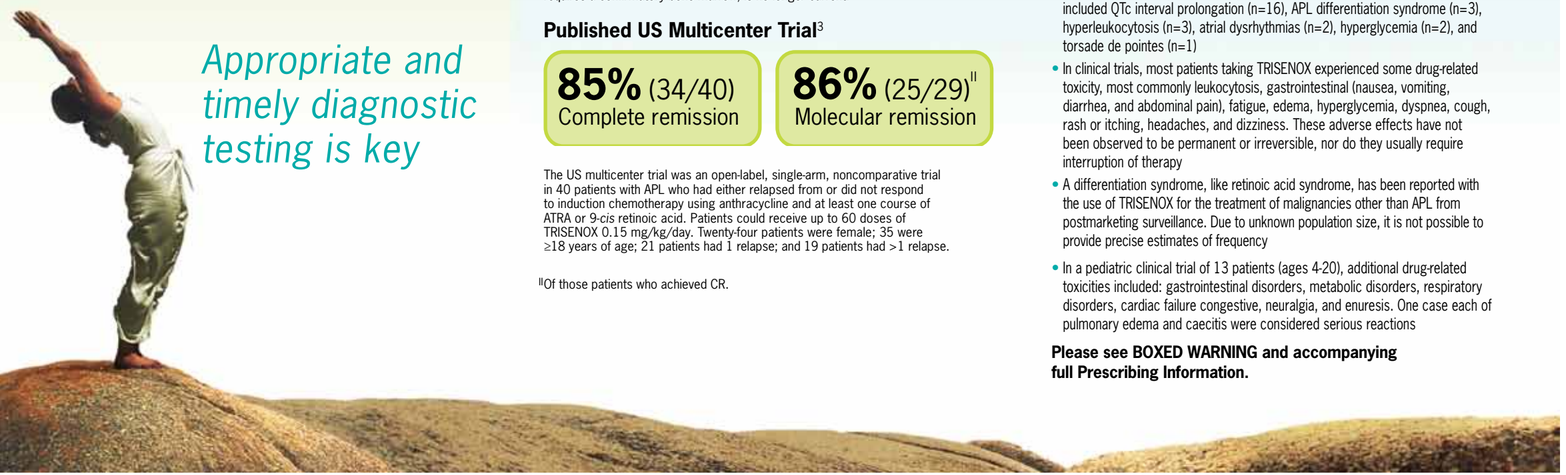
Think APL First

Identify relapsed or refractory APL patients quickly and definitively

Recognizing APL in your acute myeloid leukemia (AML) patient population can make all the difference.

- APL should be your first differential diagnosis for any patient with its signs and symptoms
- Prompt treatment of relapsed or refractory APL has the potential to improve patient outcomes[2,3]

- Relapsed or refractory APL is a medical emergency,[2] so timing is crucial
- Molecular testing can quickly and definitively diagnose APL[1]
- It is essential to determine APL markers—M3 cell morphology and t(15;17) translocation or PML/RAR-alpha gene expression—as soon as possible and to evaluate for the possibility of M3 variant[1]
- Please see the National Comprehensive Cancer Network (NCCN) Guidelines for details of recommended reverse transcriptase-polymerase chain reaction (RT-PCR) testing[1]



Appropriate and timely diagnostic testing is key

Think TRISENOX for Relapsed or Refractory APL

Successful patient management with complete courses of induction and consolidation treatment

TRISENOX induced a high rate of molecular remission (MR)* in patients who achieved CR.[3]

*Defined as the absence of PML/RAR-alpha transcript.[3]

US Multicenter Trial/Prescribing Information[5]

70% (28/40) Complete remission†

79% (22/28) Molecular remission‡

†Complete remission, as defined in the Prescribing Information: absence of visible leukemic cells in bone marrow and peripheral recovery of platelets and white blood cells with a confirmatory bone marrow ≥30 days later.[5]

‡In patients who met the criteria for complete remission, molecular remission monitored by reverse transcriptase-polymerase chain reaction to detect PML/RAR-alpha transcripts.[5]

Published results

Published remission rate data below have been adjusted based on the revised definition of remission.[4§]

§The definition was revised by the International Working Group of investigators in Madrid, Spain, 2001. The definition given in the Prescribing Information, which requires a confirmatory bone marrow, is no longer current.[4]

Published US Multicenter Trial[3]

85% (34/40) Complete remission

86% (25/29)‖ Molecular remission

The US multicenter trial was an open-label, single-arm, noncomparative trial in 40 patients with APL who had either relapsed from or did not respond to induction chemotherapy using anthracycline and at least one course of ATRA or 9-*cis* retinoic acid. Patients could receive up to 60 doses of TRISENOX 0.15 mg/kg/day. Twenty-four patients were female; 35 were ≥18 years of age; 21 patients had 1 relapse; and 19 patients had >1 relapse.

‖Of those patients who achieved CR.

Induction Treatment With TRISENOX

- **In a multicenter study, the median time to bone marrow remission (BMR) in patients treated with TRISENOX was 44 days; median time to onset of CR was 53 days**[5]
- Total induction treatment with TRISENOX can consist of up to 60 doses,[5] offering flexibility in treatment to CR and MR
- Administer TRISENOX intravenously at a dose of 0.15 mg/kg daily until BMR (total induction dose should not exceed 60 doses)[5]
- To achieve optimal clinical benefits, complete appropriate induction dosing regimen[3]

Consolidation Treatment With TRISENOX

- **Complete appropriate consolidation dosing regimen to obtain optimal clinical benefits**[3]
- Administer TRISENOX intravenously at a dose of 0.15 mg/kg daily for 25 doses over a period of up to 5 weeks[5]
- Begin TRISENOX treatment 3 to 6 weeks after completion of induction therapy[5]
- In a multicenter trial, 86% of patients who achieved CR converted to negative for the presence of PML/RAR-alpha transcript after induction (n=14) or subsequent consolidation (n=11)[3]

Indication and Important Safety Information

- TRISENOX is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression
- Serious adverse events, grade 3 or 4, were common. Those events attributable to TRISENOX in the phase 2 study of 40 patients with refractory or relapsed APL included QTc interval prolongation (n=16), APL differentiation syndrome (n=3), hyperleukocytosis (n=3), atrial dysrhythmias (n=2), hyperglycemia (n=2), and torsade de pointes (n=1)
- In clinical trials, most patients taking TRISENOX experienced some drug-related toxicity, most commonly leukocytosis, gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), fatigue, edema, hyperglycemia, dyspnea, cough, rash or itching, headaches, and dizziness. These adverse effects have not been observed to be permanent or irreversible, nor do they usually require interruption of therapy
- A differentiation syndrome, like retinoic acid syndrome, has been reported with the use of TRISENOX for the treatment of malignancies other than APL from postmarketing surveillance. Due to unknown population size, it is not possible to provide precise estimates of frequency
- In a pediatric clinical trial of 13 patients (ages 4-20), additional drug-related toxicities included: gastrointestinal disorders, metabolic disorders, respiratory disorders, cardiac failure congestive, neuralgia, and enuresis. One case each of pulmonary edema and caecitis were considered serious reactions

Please see BOXED WARNING and accompanying full Prescribing Information.

Optimal Convenience
Patient Checklist for TRISENOX® (arsenic trioxide) injection Therapy

Patient _____ Date _____

Patient ID# _____ Diagnosis _____

Monitoring Guidelines

Monitor 12-lead ECGs at baseline, then weekly

- Monitor more frequently in patients at risk for a cardiac event or if QT increases
- Avoid concomitant drugs that prolong QT interval; check online at www.azcert.org/medical-pros/drug-lists/drug-lists.cfm. Please note that this may not be a comprehensive list of all drugs
- If absolute QT is >500 msec, immediately correct risk factors such as electrolytes and concomitant drugs. The risk/benefit of continuing versus suspending TRISENOX therapy should be considered
  - If syncope, or rapid or irregular heartbeat occurs, hospitalize and monitor continuously; assess and correct electrolytes
  - Hold TRISENOX until QTc is <460 msec, electrolyte abnormalities are corrected, and the syncope and irregular heartbeat cease

Check medications*

- Current medications should be checked for QT-prolonging effect (some drugs that cause QT prolongation are listed at www.azcert.org)

Electrolytes: Monitor throughout treatment

- Monitor at least twice weekly during induction, then at least once weekly during consolidation. Clinically unstable patients should be monitored more frequently
  - Supplement electrolytes as needed
- Maintain serum potassium >4.0 mEq/L
- Maintain serum magnesium >1.8 mg/dL

Other blood tests

- Hematologic and coagulation profiles should be monitored at least twice weekly and more frequently for clinically unstable patients during induction, and at least weekly during consolidation
- TRISENOX may increase blood sugar levels
- Exercise caution in patients with renal and/or hepatic impairment
- Patients with severe hepatic and/or renal impairment should be closely monitored for toxicity when treated with TRISENOX, and a dose reduction may be warranted in the case of severe renal impairment

TRISENOX Treatment Schedule

Wt:_____ kg X _____ dose in mg/kg = _____ mg (dose of TRISENOX) (kg = lbs ÷ 2.2)

- ☐ Premedications are usually unnecessary when administering TRISENOX. However, consult your practice or institutional guidelines for more information
  - Dilute with 100 mL to 250 mL 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP. Administer IV over 1 to 2 hours. The infusion duration may be extended up to 4 hours if acute vasomotor reactions are observed

Review side effects† with patient (see nurse's notes)

Most significant

- ☐ Differentiation syndrome: Signs include unexplained fever, weight gain, dyspnea, abnormal breath sounds. Patient's weight should be checked daily
  - Intervention: Dexamethasone 10 mg IV twice daily X 3 days or longer until signs and symptoms abate
- ☐ Hyperleukocytosis: Intervention with additional chemotherapy is not recommended
- ☐ QT prolongation: Monitor electrolytes and concomitant medications carefully

Most common adverse reactions

- ☐ Leukocytosis
- ☐ Abdominal pain
- ☐ Nausea/vomiting (mild)
- ☐ Diarrhea
- ☐ Fatigue
- ☐ Edema
- ☐ Hyperglycemia
- ☐ Dyspnea
- ☐ Cough
- ☐ Rash
- ☐ Headache
- ☐ Dizziness

*Medications should be checked with each dose and at baseline.
†Adverse events are normally reversible and generally do not require interruption of therapy.

TRISENOX is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.

IMPORTANT SAFETY INFORMATION

WARNING

Experienced Physician and Institution: TRISENOX (arsenic trioxide) injection should be administered under the supervision of a physician who is experienced in the management of patients with acute leukemia.

APL Differentiation Syndrome: Some patients with APL treated with TRISENOX have experienced symptoms similar to a syndrome called the retinoic-acid-acute promyelocytic leukemia (RA-APL) or APL differentiation syndrome, characterized by fever, dyspnea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis. This syndrome can be fatal. The management of the syndrome has not been fully studied, but high-dose steroids have been used at the first suspicion of the APL differentiation syndrome and appear to mitigate signs and symptoms. At the first signs that could suggest the syndrome (unexplained fever, dyspnea and/or weight gain, abnormal chest auscultatory findings or radiographic abnormalities), high-dose steroids (dexamethasone 10 mg intravenously BID) should be immediately initiated, irrespective of the leukocyte count, and continued for at least 3 days or longer until signs and symptoms have abated. The majority of patients do not require termination of TRISENOX therapy during treatment of the APL differentiation syndrome.

ECG Abnormalities: Arsenic trioxide can cause QT interval prolongation and complete atrioventricular block. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia, which can be fatal. The risk of torsade de pointes is related to the extent of QT prolongation, concomitant administration of QT-prolonging drugs, a history of torsade de pointes, pre-existing QT interval prolongation, congestive heart failure, administration of potassium-wasting diuretics, or other conditions that result in hypokalemia or hypomagnesemia. One patient (also receiving amphotericin B) had torsade de pointes during induction therapy for relapsed APL with arsenic trioxide.

ECG and Electrolyte Monitoring Recommendations: Prior to initiating therapy with TRISENOX, a 12-lead ECG should be performed and serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed; pre-existing electrolyte abnormalities should be corrected and, if possible, drugs that are known to prolong the QT interval should be discontinued. For QTc greater than 500 msec, corrective measures should be completed and the QTc reassessed with serial ECGs prior to considering using TRISENOX. During therapy with TRISENOX, potassium concentrations should be kept above 4 mEq/L and magnesium concentrations should be kept above 1.8 mg/dL. Patients who reach an absolute QT interval value >500 msec should be reassessed, and immediate action should be taken to correct concomitant risk factors, if any, while the risk/benefit of continuing versus suspending TRISENOX therapy should be considered. If syncope, rapid or irregular heartbeat develops, the patient should be hospitalized for monitoring, serum electrolytes should be assessed, TRISENOX therapy should be temporarily discontinued until the QTc interval regresses to below 460 msec, electrolyte abnormalities are corrected, and the syncope and irregular heartbeat cease. There are no data on the effect of TRISENOX on the QTc interval during the infusion.

- Serious adverse events, grade 3 or 4, were common. Those events attributable to TRISENOX in the phase 2 study of 40 patients with refractory or relapsed APL included QTc interval prolongation (n=16), APL differentiation syndrome (n=3), hyperleukocytosis (n=3), atrial dysrhythmias (n=2), hyperglycemia (n=2), and torsade de pointes (n=1)
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For more information about TRISENOX, visit www.TRISENOX.com.
See full Prescribing Information attached to the back of this tear pad.

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Trisenox® (arsenic trioxide) injection

TRISENOX Flow Sheet	Patient
Date	
Dosing	
Weight (kg) (monitor weight gain for signs and symptoms of differentiation syndrome)	
Dose (mg) of TRISENOX	
Cardiac	
QT Interval (msec) (monitor QTc/QT interval if >500 msec; see previous page)	
Premedications	
Labs	
Chemistries	
K^+ (monitor K^+ >4.0 mEq/L)	
Mg^{++} (monitor Mg^{++} >1.8 mg/dL)	
Glucose	
Creatinine	
LDH	
SCPT/SGOT	
ALK PHOS	
Hematology	
WBC	
ANC	
Hemoglobin (g/dL)	
Hematocrit	
Platelets	
Treatments	
RBC transfusion	
Platelet transfusion	
Growth factors	
Other	
Initials	