Clinical Experience of Arsenic Trioxide in Relapsed Acute Promyelocytic Leukemia

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ABSTRACT

Acute promyelocytic leukemia (APL) has unique clinical, cytogenetic, and molecular features and is one of the most potentially curable human malignancies. The current standard treatment given to patients with newly diagnosed APL consists of all-trans retinoic acid and anthracycline-based cytotoxic chemotherapy, which is highly effective for remission induction. However, despite the potential for cure with existing treatments, approximately 20%-30% of patients relapse and require salvage therapy. Reports of the safety and efficacy of arsenic trioxide from centers in China led to a pivotal trial of this agent in the United States for patients with relapsed APL. In an initial pilot study, 11 of 12 patients experienced a complete response, and a subsequent multicenter trial confirmed the efficacy and safety of arsenic trioxide for remission induction in this patient population. Additional trials are under way to evaluate the use of this agent alone or as part of a chemotherapy regimen for consolidation and maintenance of patients with APL.

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INTRODUCTION

Acute promyelocytic leukemia (APL) French American and British (FAB) M3) is a distinctive type of acute myelogenous leukemia and represents approximately 10%-15% of adult myeloid leukemias [1]. The annual incidence of newly diagnosed APL in the United States is approximately 1,000 to 1,500 cases; another 2,500 to 4,000 cases occur outside the United States. Although relatively uncommon, APL has been the subject of intensive interest because of its distinctive clinical, morphologic, cytogenetic, and molecular properties.

First recognized as a distinct clinical entity in the 1950s, APL is characterized by a severe coagulopathy, high early mortality, and peripheral blood and bone marrow dominated by abnormal heavily granulated promyelocytes [2]. The bleeding diathesis of APL is associated with a high potential for early hemorrhagic death and is present in the majority of these patients at the time of their initial diagnosis requiring aggressive management with platelet and fresh/frozen plasma transfusions [3]. Multifactorial in etiology, the bleeding propensity is caused by a combination of disseminated intravascular coagulation and hyperfibrinolysis [4]. Induction therapy with cytotoxic chemotherapy can precipitate or exacerbate the coagulopathy, because lysis of the hypergranular leukemic promyelocytes releases their content (tissue factor and procoagulants) into the plasma, resulting in the consumption of the clotting factors. Fibrinolysis may be caused by increased expression by the leukemic cells of annexin II, a receptor for fibrinolytic proteins, and decreased activity of thrombin-activatable fibrinolysis inhibitor [4, 5].

Before the early 1990s, therapy for APL consisted of an anthracycline antibiotic plus cytosine arabinoside for induction, followed by additional cycles of chemotherapy for consolidation and/or maintenance [6]. This standard approach resulted in complete remissions (CRs) in 60%-80% of patients; 5-year survival rates were 20%-30% [6]. Since the incorporation of all-trans retinoic acid (ATRA) into the treatment regimen in the early 1990s, the overall and disease-free survival of patients with APL has increased by nearly twofold, in addition to an increased CR rate [1, 6]. However, 20%-30% of patients with APL relapse despite this advancement [7]. Salvage therapy for these patients entailed high doses of cytotoxic chemotherapy, treatment that is often toxic and rarely curative. Bone marrow transplantation, although potentially curative, is an
option for only a fraction of the younger relapsed patients. An initial pilot study and a subsequent confirmatory multicenter trial of arsenic trioxide (Trisenox™) in patients with relapsed APL demonstrated a high rate of CRs that included molecular remissions in over half the patients after receiving one to two cycles of therapy. This article discusses the background, evaluation, and clinical utility of the use of this agent in patients with APL.

**Cytogenetic Features and Molecular Pathogenesis of APL**

In the 1970s, patients with APL were found to have abalanced and reciprocal translocation involving the long arms of chromosomes 15 and 17, t(15;17)(q22;q21) [8]. This translocation is virtually diagnostic for this subtype of acute myelogenous leukemia. At a molecular level, this cytogenetic abnormality reflects disruption of the promyelocytic leukemia gene (PML) on chromosome 15 and the retinoic acid receptor-α gene (RAR-α) on chromosome 17 [9-11]. The resultant fusion gene, t(15;17), encodes the chimeric proteins PML/RAR-α and RAR-α/PML. The former is found in nearly all patients with the t(15;17) translocation, whereas the latter is detected in about two-thirds of patients [12]. Small numbers of patients with clinical APL lack this specific cytogenetic abnormality. In these rare cases in which no PML involvement can be found, the RAR-α gene is linked to the promyelocytic leukemia zinc finger on chromosome 11, nucleophosmin on chromosome 5, or the nuclear mitotic apparatus protein gene on chromosome 11 [13].

In addition to their well-known effects on vision, retinoids are prime regulators of cell proliferation and differentiation and have a critical role in embryonic morphogenesis [12]. Two families of retinoic acid receptors, each with three subtypes, RAR-α, -β, -γ, and RXR-α, -β, -γ, regulate transcription of target genes [14]. Only the RARs are activated bycomplexing with retinoic acid. The RAR-α translocation plays a strong role in the pathogenesis in APL, by interfering with the physiological activity of the normal RAR-α protein and exerting a dominant negative effect [9, 15]. As a result, the fusion protein disrupts direct transcriptional control of certain primary target genes, interferes with other transcriptional factors, and exerts post-transcriptional effects such as the induction of transforming growth factor β [16]. Ultimately myeloid differentiation is inhibited, leading to the accumulation of the leukemic cells at the promyelocytic stage of development.

**Current Therapeutic Approaches in the Management of APL**

Since the introduction of ATRA into the upfront APL treatment regimen, CR rates as well as disease-free survival have improved significantly. However, newer therapies are needed for patients who fail to respond or who relapse after treatment with current standard therapy.

**ATRA-Based Therapy**

**Role of Retinoids in APL Therapy**

In 1978, Sachs reported that cells from a murine leukemic cell line could be induced from an immature to a mature phenotype [17]. Subsequently, Breitman et al. found that exposure to ATRA could induce differentiation in HL-60 cells, a cell line with elements resembling leukemic promyelocytes but lacking t(15;17) [18]. In the latter part of the 1980s, treatment of APL was revolutionized when Chinese investigators reported that a high proportion of patients treated with capsules of ATRA achieved CRs [19]. The success of ATRA is believed to be due to its ability to induce differentiation of the leukemic clone. Pharmacologic doses of ATRA degrade the aberrant fusion protein, thereby overcoming the dominant negative effect of PML/RAR-α fusion proteins [15].

**ATRA as Single-Agent Therapy**

Clinical trials of single-agent ATRA have reported CR rates ranging between 50%-80%—a rate comparable to that achieved with standard cytotoxic chemotherapy [20]. Patients treated with this approach would be expected to undergo remission without an interval of aplasia or a worsening of the coagulopathy seen with standard chemotherapy. However, the duration of remission in patients treated with ATRA alone has been relatively brief, and essentially all patients relapse within 10 months [21]. Therefore, ATRA is administered as a standard component of combination chemotherapy with an anthracycline antibiotic in patients with APL [22].

**Chronology of ATRA Administration**

Although the inclusion of ATRA with standard chemotherapy appeared likely to improve outcomes, the optimal schedule of administration of the two treatments was unclear. Several studies were conducted to determine the optimal ATRA/chemotherapy induction regimen in patients with APL [6, 23-26]. In a large randomized trial comparing sequential versus concurrent ATRA and chemotherapy, CR occurred in 381 patients (92%), with similar proportions of patients in both treatment groups experiencing CR. At 2 years follow-up, significantly more patients in the sequential group than in the concurrent group had relapsed (16% versus 6%; p = 0.04). Also, the addition of chemotherapy to ATRA at the initiation of treatment led to CR rates higher than 90%. Furthermore, recent trials
have shown a benefit for maintenance therapy with ATRA, with or without low-dose chemotherapy, suggesting it be indicated for all patients with APL [27].

**ATRA Plus Chemotherapy Followed by Hematopoietic Stem Cell Transplantation as Salvage Therapy**

The optimum postremission therapy for patients with APL has not yet been defined. For the approximately 20%-30% of patients who relapse, treatment with ATRA and/or chemotherapy can usually produce a second CR, but stem cell transplantation may provide greater benefit. This approach was tested in a population of patients who relapsed and achieved a second CR with ATRA followed by timed etoposide/mitoxorotone/cytosine arabinoside therapy [28]. After CR, patients underwent myeloablation followed by either autologous or allogeneic (HLA-compatible donor and < 55 years of age) transplant. Although the combination of ATRA and etoposide/mitoxorotone/cytosine arabinoside was effective in the treatment of relapsed APL, allogeneic transplantation in this setting was associated with significant toxicity and high mortality. However, the results of autografting were encouraging, with a 3-year disease-free survival of 77%.

**ARSENIC TRIOXIDE-BASED THERAPY**

**Role of Arsenicals in Leukemia Therapy**

Since ancient Greek and Roman civilizations, arsenic has been an active ingredient in the folk remedies of central and southern Asia [29]. In 1878, a formulation of arsenic (Fowler’s solution) was first used to treat leukemia [30]. In 1992, Sun et al. in China described 32 cases of morphologic APL (not confirmed by cytogenetics or reverse transcrip-tase polymerase chain reaction [RT-PCR]) treated with Ailing-1, a Chinese herbal arsenical preparation [31]. Of the initial cases, 16 of 32 (50%) survived more than 5 years without any anthracycline-based therapy. This and other studies from China stimulated intensive investigation on the role of arsenic trioxide in the treatment of APL and other malignancies [32-34].

The mechanisms behind the effects of arsenic therapy for APL are not completely understood. Studies on APL-derived cell lines and transgenic mice carrying the PML/RARα fusion proteins indicate that arsenic trioxide induces degradation of both the chimeric PML/RAR-α and native PML from the nuclei of the malignant cells [35, 36]. This allows partial differentiation of the leukemic population to proceed [36]. Arsenic trioxide also induces apoptosis possibly by indirectly impairing H2O2 catabolism with a resultant decrease in mitochondrial membrane potential, release of cytochrome c, and activation and upregulation of caspases 1, 2, 3, and 8, [1, 37, 38].

**Arsenic Trioxide in Relapsed and Refractory Patients**

After the Chinese reports of the efficacy of arsenic trioxide in APL, in 1997 a pilot study of this compound was initiated in 12 relapsed patients (Table 1) [1]. Of the 12

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<tr>
<th>Patient</th>
<th>Age (y)</th>
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*Retinoid resistant.
†Treated with chemotherapy: patients 2, 3, and 8 (mitoxantrone and etoposide) and patient 10 (methotrexate, vincristine, and mercaptopurine).
‡Previously treated with allogeneic bone marrow transplantation.
§Also treated with 9-cis-retinoic acid plus a monoclonal antibody to CD33.
||Died of an intracerebral hemorrhage on day 5.

Modified with permission [1].
patients, 11 (92%) had a CR after treatment ranging from 12 to 39 days (median, 33 days). Median daily dose was approximately 0.16 mg/kg (range, 0.06-0.20 mg/kg), and the median cumulative dose was 360 mg (range, 160-515 mg); this dosage was similar to that reported by the Chinese investigators. In addition to the high CR rate, 8 of the 11 patients who initially tested positive for PML/RAR-α by RT-PCR later became negative. The above results were supported and extended by follow-up from the U.S. pilot and multicenter trials [39]. Combining the results from the pilot and multicenter studies, the CR rate was 87% (45 of 52), with a molecular conversion rate from positive to negative for the PML/RAR-α transcript of 78% [40]. Of the 45 patients achieving a CR, 31 (69%) remained alive at a median follow-up of 18 months.

Adverse events reported with arsenic trioxide include leukocytosis, the APL differentiation syndrome, QT prolongation on electrocardiogram, peripheral neuropathy, hyperglycemia, and skin reactions. The APL differentiation syndrome, which is clinically identical to the previously named retinoic acid syndrome, was observed in approximately 30% of the APL patients treated with arsenic trioxide for remission induction. The syndrome consists of one or more of the following signs or symptoms: fevers, skin rash, peripheral edema, pulmonary infiltrates, and plural or pericardial effusions [41]. This syndrome is effectively treated with dexamethasone if treatment is initiated at the first sign or symptom.

Asymptomatic QT prolongation on electrocardiogram was seen in over half the patients treated with arsenic trioxide. The management of QT prolongation consisted of maintaining serum potassium levels >4.0 mEq/dl, and magnesium levels >1.8 mg/dl. If the QTc is >500 msec, corrective actions should be taken, including telemetry monitoring, and the risk/benefits of continuing therapy should be considered. Other adverse events included peripheral neuropathy, lightheadedness during the infusion, fatigue, musculoskeletal pain, and mild hyperglycemia. Toxicities were manageable and similar to those described in the pilot.

The investigators concluded that arsenic trioxide is highly effective for clinical and molecular remission induction in patients with relapsed APL. Consequently, patients can be offered additional strategies, including autologous or allogeneic stem cell transplantations and/or consolidation chemotherapy to increase their long-term, disease-free survival.

SUMMARY AND CONCLUSIONS

The introduction of ATRA has significantly improved the disease-free and overall survival in patients with APL.

Currently, ATRA remains first-line therapy in patients presenting with de novo APL. However, the studies presented herein confirm reports from China of the striking efficacy and safety of arsenic trioxide in the treatment of APL. In addition, patients treated with arsenic trioxide had a high rate of molecular conversion to PML/RAR-α negativity.

Arsenic trioxide fulfills an unmet medical need based on its ability to induce CR in patients with relapsed APL. The safety profile of the drug is favorable. Adverse events are uncommon, generally self-limiting, and reversible. Therapy with arsenic trioxide offers the opportunity for a CR and improved survival in patients with refractory/relapsed APL (Fig. 1). In the future, the role of this compound will be evaluated as both a single agent or in combination with chemotherapy for the consolidation and maintenance treatment of patients with APL.
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