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Review

Clinical Implementation of Arsenic Trioxide

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ABSTRACT

Introduction of arsenic trioxide (ATO, As_2O_3) to the treatment of acute promyelocytic leukemia in the 1970s enlightened an effective treatment approach for the disease. Decades later, knowledge on this agent's further functions has rapidly advanced so that it has entered common use in hematology and oncology. In addition, As_2O_3 reportedly induces DNA and chromosomal damage, inhibits DNA repair, and alters DNA methylation in mammalian cells. The compound is becoming increasingly reasonable as a treatment modality to rectify genetic blood disorders and other cancer types. Nevertheless, limitations of As_2O_3 typically emerged from drug resistance, adverse effects and secondary tumors, which may result in a myriad of outcomes. Though prolonged exposure to As_2O_3 ensues poisons and genome alternations that do not permanently change the DNA sequence, other synergistic alterations should be considered as replacement. In this review, we recollect the discovery and clinical implementation of As_2O_3, describe its advantages and shortcomings for leukemia and solid cancer treatment, and consider future prospects for engendering useful impacts.

Key words
acute promyelocytic leukemia; advantages; arsenic trioxide; shortcomings; side effects; therapeutics

1. Introduction

Arsenic trioxide (ATO, As_2O_3) was first found to be effective in the treatment of acute promyelocytic leukemia (APL) at the First Affiliated Hospital of Harbin Medical University (FAHHMU) in China in the 1970s (Zhang et al, 1984). Afterwards it has been studied as a potent choice for APL patients worldwide, a safe and effective anti-APL therapy of both long- and short-term (Zhou et al, 2010b; Wang et al, 2014). Current opinions regard it as the most effective single reagent for APL treatment (Daver et al, 2015; Coutre et al, 2014; Seftel et al, 2014). Following the discovery of immense potential cytotoxicity of ATO in solid malignant tumors including the breast cancer, the lung cancer, neurogliomas, etc., we are trying to learn more functions of this traditional Chinese medicine (Cheng et al, 2016; Jiang et al, 2004; Chow et al, 2004).

In spite of being poisons, arsenic metabolites have been proved to increase cellular reactive oxygen species (ROS) as a potential inducer of genomic instability through DNA damage,

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DNA repair or telomere dysfunction (Kryeziu et al, 2016; Woo et al, 2002). The DNA damage induced by these modalities can silence tumor suppressors such as pro-apoptotic genes or activate proto-oncogenes that in turn lead to genomic instability and cellular transformation, and apoptosis is eventually induced. The cell apoptosis in response to ATO can decrease mitochondrial membrane potential and increase caspase-3 activation and DNA fragmentation. However, ATO as a double-edged sword can strongly damage DNA sequences, leading to a myriad of adverse effects that include cancers of the skin, the lung, the liver, and the bladder (Bhattacharjee et al, 2013; Andrew et al, 2009; Burgdorf and Hoenig, 2014).

APL (acute myelocytic leukemia-M3) is characterized with cytogenetic abnormality of *t* (15;17) translocation and PML-RARα fusion oncoprotein. ATO at a low dose can induce cell differentiation by targeting the PML-RARα protein, whereas at a high dose induced apoptosis. Here we reviewed the anticancer history of ATO, described its advantages and shortcomings for leukemia and solid cancer treatment, and considered future prospects for engendering useful impacts.

2. Milestones of development of ATO as a remedy for APL

2.1 Discovery of therapeutic efficacy of ATO for leukemia

ATO, called *Pi Shuang* in TCM with serious toxicity, has a medicinal history of over 2400 years in China. It is used to treat malignancies based on the "like cures like" principle in TCM. However, not until 1970s has ATO been purposely used to treat leukemia patients. The person who first discovered the effectiveness of ATO in fighting leukemia is Ting-dong Zhang, a Chinese physician and scientist at FAHHMU. His group used the ATO injection to treat six leukemia patients and carried out clinical observation at FAHHMU. The results were reported in *Heilongjiang Medical Journal* in 1973, entitled "Primary clinical observation on six cases of acute promyelocytic leukemia with treatment of AILING injection" that is the first paper on ATO treatment for leukemia patients in which the chemical composition and application of ATO were described in detail (Zhang et al, 1973).

2.2 Validation of ATO for treatment of APL in small-scale clinical trials

After this discovery, Zhang spent a few years on ATO treatment for acute myelocytic leukemia (AML). In 1979, Zhang et al reported that ATO was highly effective in "promyelocytic type" with the total remission rate of 70% in 55 AML patients administrated with ATO (Zhang, 1979). In 1984, Zhang reported that 22 AML patients including 15 APL obtained CR after ATO treatment at FAHHMU (Zhang, 1984). Those findings were paid great attention by both physicians and researchers in China.

2.3 Introduction of ATO treatment for APL to Western medicine

Clinical applications and laboratory experimentations of more than 20 years showed the effectiveness of ATO in the treatment of leukemia in China, however, not until 1996 has ATO treatment for APL been known worldwide. During 1996 to 1997, Zhu Chen of Shanghai Rui Jin Hospital reported the molecular mechanism of ATO treatment for APL. So researchers can clearly understand the way ATO works.

In 1996, Chen et al demonstrated that ATO induces NB4 cell apoptosis with down regulation of Bcl-2 expression and modulation of PML-RAR alpha/PML proteins, which were published in *Blood* (Chen et al, 1996). These experiments were reproduced in cultured primary APL cells, all-trans retinoic acid (ATRA)-susceptible (NB4 cells), and ATRA-resistant (MR2 subclone) APL cell lines (Chen et al, 1997).

In 1997, Wang and Chen investigated the clinical efficacy and pharmacokinetics of ATO in relapsed APL patients. The paper entitled "Use of arsenic trioxide (As_2O_3) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients" published in Blood, is the first English paper on the extraordinary therapeutic efficacy of ATO in treating APL (Shen et al, 1997). This report showed that 14 of 15 relapsed APL patients, including two at the second and two at the third relapse, achieved CR after ATO treatment. The results are of particular significance in clinic, since relapsed APL patients have relatively poor prognosis, leading ATO treatment for APL famous to the world. Due to its anti-leukemia bioactivity, the drug Trisenox PolaRx was produced by Biopharma-ceuticals that was approved by the US FDA in the year of 2000 and subsequently marketed and sold by Cephalon. Ever since then, ATO has been worldwide used for the treatment of APL that is unresponsive to ATRA, and the joint therapy of ATO and ATRA has also been approved by FDA for the treatment of certain leukemias. After that ATO treatment for APL was accepted by the Western world.

2.4 Control of side effects of ATO in treatment of APL

Due to the toxicity, ATO risk was gradually unraveled in its clinical applications. The side-effects of ATO include hematologic toxicity, cardiac toxicity, neurologic toxicity, and hepatic toxicity. They were described in detail in Part 4. It is urgent to control side effects of ATO in order to ensure the clinical safety and therapeutic efficacy. So we developed a new ATO-delivering method in 2004, namely "continuously slow ATO intravenous infusion", a successful avoidance from toxicities of ATO (Zhou et al, 2005; 2004) described in detail in Part 5.

3. Advantages of ATO in treatment of APL

3.1 Clinical studies in relapsed APL

ATO started to be used in the treatment of relapsed APL