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Arsenic Trioxide and Leukemia

From Bedside to Bench

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Summary

Cumulative evidence indicates that traditional Chinese medicine (TCM) is an important resource for discoveries of drugs against cancer. Arsenic, a common, naturally existing substance, is rarely found in its pure elemental state in nature. In addition to the organic arsenicals, there are three major inorganic arsenic forms: red arsenic (As$_2$S$_3$), yellow arsenic (As$_2$S$_5$), and white arsenic (As$_2$O$_3$, ATO). Based on the basic TCM theory of “using poison against poison,” a group from Harbin Medical University in the northeastern region of China in the early 1970s introduced intravenous infusion of “Ailing-1 (anticancer-1),” a solution of crude ATO and herbal extracts, into cancer therapy. After a lengthy study in more than 1000 patients with various kinds of cancers, acute promyelocytic leukemia (APL), a specific subtype of acute myeloid leukemia characterized by the failure of differentiation/maturation towards granulocytic cells at the promyelocytic stage, was determined to be an excellent target for “Ailing-1” therapy. At the same time, there were reports of using the formula called “niu huang jie du pian” (containing xiong huang) or just using xiong huang (realgar) by itself to treat APL. A formula of Qing Dai (indigo) containing xiong huang as the main Chinese herb was reported to result in 98.3% total remission.

Thus, some cautious clinical trials with pure ATO and state-of-the-art bench studies were conducted worldwide. The results revealed that ATO brings the majority of relapsed APL patients to a second complete morphologic, cytogenetic, and even molecular remission. Successful experiences that used ATO together with the differentiation-inducing agent all-trans retinoic acid (ATRA) and chemotherapeutic drugs make APL the most curable subtype of acute myeloid leukemia in adults, an unprecedented achievement in the field of hematologic malignancies. The clinical data from our group showing striking efficacy and safety of ATO in patients with APL led to clinical trials in the United States and subsequent approval by US Food and Drug Administration (FDA) in September 2000. Inspired by such a bedside discovery, many investigators are researching pharmacological mechanisms of ATO, and finding that ATO exerts wide-spectrum cellular and molecular activities on APL cells and other cancer cells, such as growth arrest, apoptosis induction, differentiation induction, and anti-angiogenesis, although its exact mechanisms remain to be determined. More importantly, the clinical potential of ATO in other cancers beyond APL is also under study. In this chapter, we discuss recent clinical practice and the mechanism of ATO action on APL and other cancer cells.

Key Words: Arsenic trioxide; acute promyelocytic leukemia (APL); clinical trials; differentiation; apoptosis; leukemia; cancer.

1. Introduction

Microbial and plant secondary metabolites helped to double our life span during the twentieth century, reduced pain and suffering, and revolutionized medicine. For instance,
all-trans retinoic acid (ATRA), a vitamin A derivative, has been successfully used for acute promyelocytic leukemia (APL) by inducing terminal differentiation of leukemic cells towards granulocytes, the only well-established example of cancer differentiation therapy so far (1,2). In the past 20 yr, a therapeutic strategy with ATRA and anthracycline-based chemotherapy for induction, anthracycline-based consolidation, and maintenance with ATRA and/or low-dose chemotherapy has kept more than 70% of APL patients alive and disease-free for 5 yr, an unprecedented achievement in the field of oncology (3).

Increasing evidence demonstrated that herbs-based traditional Chinese medicine (TCM) could be used for treatment of many diseases, including cancer. As documented, some Chinese herbs, such as Qing Dai (Indigo naturalis), Ya Dai Zi (Brucel javanica), She Xiang (Moschus moschiferus), and E Shu (rhizoma Curcuma phaeocaulis), can directly kill cancer cells. Also, other herbs can inhibit cancer cell growth, such as Jiang Huang (Curcuma aromatica), Chang Chun Teng (Hedera helix), Tian Hua Feng (Trichosanthes kirilowii), Tian Nan Xing (Arisaemi japonicum), and Shan Zi Gu (Cremastra variabilis) (4,5). In addition, up to 100 kinds of Chinese herbs can stimulate the patient’s immune system to attack cancer cells (6). Taken together, Chinese herbs are becoming important resources for anticancer drug discovery (7).

Chinese herbs are often mixed into formulae for clinical application. For example, the formula “Qing Huang San” (one of the popular formulae that grinds two herbs, Qing Dai and Xiong Huang, at a ratio of 9:1 into fine powder, which is loaded into capsules) was shown to effectively treat chronic myeloid leukemia (CML) (8). In 1995, Huang et al. from Da Lian city, China, used a formula combining these two herbs as main ingredients to treat 60 APL patients, which resulted in 98.3% experiencing total remission (9). Before that, there were reports of using a formula called “niu huang jie du pian” (containing Xiong Huang) or just using Xiong Huang (realgar) by itself to treat APL (8).

APL, an unique subtype of acute myeloid leukemia (AML), is characterized by the blockage of granulocytic differentiation at the promyelocytic stage and specific reciprocal chromosomal translocation t(15;17)(q22;q21). The latter leads to the expression of the fusion protein PML-RARα (promyelocytic leukemia—retinoic acid receptor-α), whose leukemogenic role has been demonstrated using transgenic mouse models (10). Although conventional chemotherapy such as anthracyclines and cytosine arabinoside help about 70% of newly diagnosed APL patients to reach clinically complete remission (CR), a high frequency of early death (mainly due to exacerbation of bleeding syndrome) and a lower 5-yr disease-free survival (DFS) rate have emphasized a need for new drugs. Inspired by the Chinese philosophy that it is better to transform and reverse a bad element than to simply get rid of it, and by important discoveries in the 1970s and early 1980s that leukemic cells undergo phenotypic reversion in vitro when treated with some agents, the Shanghai Institute of Hematology (SIH) started to screen a large number of compounds. SIH identified ATRA as a strong differentiation-inducing agent for APL cells, and improved clinical efficacy as mentioned above. However, there is still a 30% relapse rate, especially in APL patients having higher white blood cells (WBC) counts. In addition, relapsed patients after ATRA treatment are resistant to this drug, which becomes the main reason for failure to be cured (11,12). Fortunately, arsenic trioxide (As2O3, ATO, commercially named Trisenox™ [Cell