In 1888, Hutchinson (5) described with utmost clarity the diagnosis and progression of arsenic-induced cancer in humans exposed for medicinal purposes: “I have two separate propositions to maintain, one of which is, however, of great importance to the other. The first is that by the prolonged internal use of arsenic the nutrition of the skin may be seriously affected, and that, amongst other changes, warty and corn-like inductions may be produced. The second goes much further and asserts that if the drug be continued these ‘arsenic corns’ may assume a tendency to grow downwards and pass into epithelial cancer.” The remainder of his remarkable article detailed case reports and correspondence surrounding the use of Fowler’s solution (1% potassium arsenite) for treating skin disorders and cancer as well as the associated arsenic-induced keratosis and secondary tumor formation.

Arsenicals have been used widely as medicinals to treat various disorders, including arthritis, asthma, psoriasis, syphilis, and cancer; these long-standing pharmacologic uses have diminished because of toxicity, and arsenicals were frequently put to nefarious uses. Nonetheless, arsenicals are still used in agriculture and industry (4).

Arsenic is a common contaminant of drinking water; thus, arsenic exposures are not uncommon. Occupational exposures to higher levels of arsenic occur, as do exposures of populations living near smelters. Cancers in humans associated with arsenic exposure include those of skin, lung, liver, gastrointestinal tract, hematopoietic system, kidney, and, possibly, urinary bladder and brain. Therefore, in arsenic, we have a potent carcinogen for a variety of organs via a variety of exposure routes.

The fact that arsenicals, when given alone, have not been shown convincingly to induce tumors in laboratory animals may indicate that humans are more sensitive to arsenic-induced cancers, an alarming prospect. In this regard, arsenic trioxide has not been tested adequately for carcinogenicity in experimental animals (6).

Whereas the use of arsenic trioxide in the chemotherapy of APL, and perhaps other hematopoietic cancers, has great clinical potential, arsenic and arsenic compounds are indeed carcinogenic to humans (3,4).

NOTES

Affiliation of authors: J. Huff, A. Nyska, P. Chan, Division of Intramural Research, National Institute of Environmental Health Sciences, Research Triangle Park, NC; M. Waalikes, Laboratory of Comparative Carcinogenesis, National Cancer Institute at National Institute of Environmental Health Sciences, Research Triangle Park.

Correspondence to: James Huff, Ph.D., Division of Intramural Research, National Institute of Environmental Health Sciences, P.O. Box 12233,
We agree with the opinion of Huff et al. (1) that “the use of arsenicals must be tempered by toxicologic realities.” Arsenic has been ranked highest in priority on a list of the top 20 hazardous substances by the Agency for Toxic Substances and Disease Registry and the U.S. Environmental Protection Agency (2). Indeed, cancers in many organs have been reported in populations living near smelters and drinking water with a contaminant of arsenic. However, arsenic alone has not been proven to induce cancer in an animal model (3). This fact implies either that humans are more sensitive to arsenic-induced cancer or to long-term exposure or that higher doses of arsenic are needed for carcinogenesis. Many proposed models of arsenic carcinogenesis tend to support a threshold relationship (2). Therefore, the medical use of arsenic under the threshold would be without higher risk for carcinogenesis.

Arsenic has been used for centuries for different medical purposes. Since 1865, Fowler’s solution (potassium arsenite) has been used for the treatment of chronic myelocytic leukemia and continued to be an important agent until the discovery of busulfan and radiation therapy. Although case reports have suggested that prolonged use of arsenites may be associated with cancers at internal sites, large cohort studies showed no increase of internal cancers in the patients treated with Fowler’s solution (3).

Several groups have confirmed the predictable induction of remission without severe toxicity by arsenic trioxide (As$_2$O$_3$) in a large series of patients with relapsed acute promyelocytic leukemia (APL). However, one group (4) reported severe toxicity in a few patients with APL. We (5) also observed unexpected severe liver toxicity in two newly diagnosed patients with APL after treatment with As$_2$O$_3$. Until now, secondary cancers have not been reported in patients with APL after treatment with As$_2$O$_3$. The low dose of As$_2$O$_3$, the method of administration (intravenous), or the duration of treatment may not have reached the threshold to induce secondary cancers. Moreover, recent pharmacokinetic studies (6) performed during and immediately after induction of remission showed that in vivo accumulation of As$_2$O$_3$ in peripheral tissues declined after withdrawal of the drug.

Whether As$_2$O$_3$ will be effective as a treatment for other forms of cancers including lymphoma is questionable. On the basis of recent mechanistic studies of As$_2$O$_3$-induced remission in APL (7), it seems that both differentiation and induction of apoptosis are involved in its therapeutic effect. As$_2$O$_3$ in vitro induces apoptosis in many tumor cell lines at clinically acceptable concentrations (1–2 μM). However, in vivo animal-tumor models are needed to evaluate its therapeutic effect because physiologic factors such as selenium may block As$_2$O$_3$-induced apoptosis (5). At the present time, As$_2$O$_3$ has been used in patients with relapsed APL and has proven to be a novel and effective therapy to prolong life. Our observation that As$_2$O$_3$ is not cross-resistant with doxorubicin (Adriamycin) and paclitaxel (Taxol) in P388/adr lymphoma with multidrug resistance supports a rationale to expand the use of this drug (5). If As$_2$O$_3$ is proven to be effective in patients with other types of cancers, like other cancer chemotherapeutic agents, then its use is justified despite potential carcinogenic risk.

SAMUEL WAXMAN
YONG-KUI JING
ZHU CHEN
GUO-QIANG CHEN

REFERENCES


NOTES

Affiliations of authors: S. Waxman, Y. Jing, Mount Sinai School of Medicine, New York, NY; Z. Chen, G.-Q. Chen, Shanghai Institute of Hematology, China.

Correspondence to: Samuel Waxman, M.D., Mount Sinai School of Medicine, Box 1178, 100th and 5th Ave., New York, NY 10029.

EDITOR’S NOTE

Guido Kroemer and Hugues de Thé declined to respond to James Huff et al.’s correspondence.