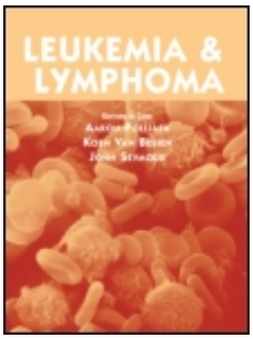

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COMMENTARY

Carcinogenic risk of retained arsenic after successful treatment of acute promyelocytic leukemia with arsenic trioxide: a cause for concern?

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The remarkable capacity of therapy that includes arsenic trioxide (ATO) to induce sustained relapse-free survival in most patients with newly presenting acute promyelocytic leukemia [1–3] results in a high probability of cure of the leukemia under circumstances where there has been exposure to the hypothetical risk of carcinogenicity from administered arsenic.

Ingestion of inorganic arsenic compounds has long been regarded to increase the risk of development of cancer, and epidemiological studies have demonstrated that the incidence of death from cancer, in particular of bladder, kidney, liver, lung and skin, undergoes a clearly defined increase after regular ingestion for approximately 20–30 years of drinking water contaminated with inorganic arsenic, primarily arsenite and arsenate [4]. The threshold for the concentration of arsenic in drinking water for an increase in cancer incidence has been estimated, in the case of skin cancer, to be of the order of 0.64 mg per liter [5], corresponding to daily ingestion of the equivalent of approximately 1 mg of ATO. ATO is relatively insoluble in the aqueous medium employed for intravenous drug administration, and is converted prior to administration for treatment of acute promyelocytic leukemia to the more soluble potassium or sodium arsenite salts that have equivalent carcinogenic properties to the inorganic arsenic ingested in drinking water, which consists predominantly of arsenite, or of arsenate that is reduced to arsenite *in vivo* (Figure 1).

The question of whether protracted retention of arsenic after successful treatment of acute promyelocytic leukemia with ATO has carcinogenic potential is the subject of the communication of Au and colleagues in this issue of the journal [7]. Development of thyroid cancer was detected in a patient who had remained in complete remission for 10 years after completion of an admittedly long period of intermittent courses of 10 mg of oral ATO per day over 24 months, compared to the overall period of intermittent exposure to ATO of approximately 5–11 months in other protocols [2,3]. The concentration of arsenic in normal thyroid tissue surrounding the excised cancer exceeded that in the normal thyroid tissue of four other patients with thyroid cancer who had no known exposure to arsenic, and was considered to reflect retention of arsenic for 10 years after completion of ATO administration that could have promoted the development of thyroid cancer.

There are a number of questions as to the extent to which these observations provide evidence of an unequivocal link between tissue retention of arsenic after ATO therapy and an increase in cancer risk. The arsenic concentration in thyroid tissue of the unexposed control subjects was highly variable, ranging from virtually negligible to approximately half that in the ATO trioxide treated patient, which in such a limited number of patients prevented statistically significant confirmation of a difference between arsenic concentrations in thyroid tissue of the patient and the subjects who had not knowingly been exposed to arsenic.

Appreciable variation in the level of arsenic in thyroid tissue has previously been reported in subjects with no known exposure to arsenic, and has been attributed to variation in environmental exposure to unrecognized sources of arsenic [8] that include seafood and drinking water. Arsenic derived from seafood ingestion contains appreciable amounts of organic chemical species such as arsenobetaine and arsenocholine that are not derived from inorganic arsenic in the human, and can be readily differentiated from the inorganic and methylated arsenic species in the human after assimilation of inorganic arsenic (Figure 1). Analysis of the arsenic compounds in the thyroid of the subjects reported by Au and colleagues with high performance liquid chromatography (HPLC) and inductively coupled mass spectrometry could have greatly assisted in resolving the extent to which arsenic in the thyroid of their patient was derived from an alternative source such as seafood, in comparison to the type of arsenic chemical species consistent with derivation from therapeutically administered ATO (Figure 1).

Another concern is that the protracted period of retention of arsenic proposed to occur after cessation of

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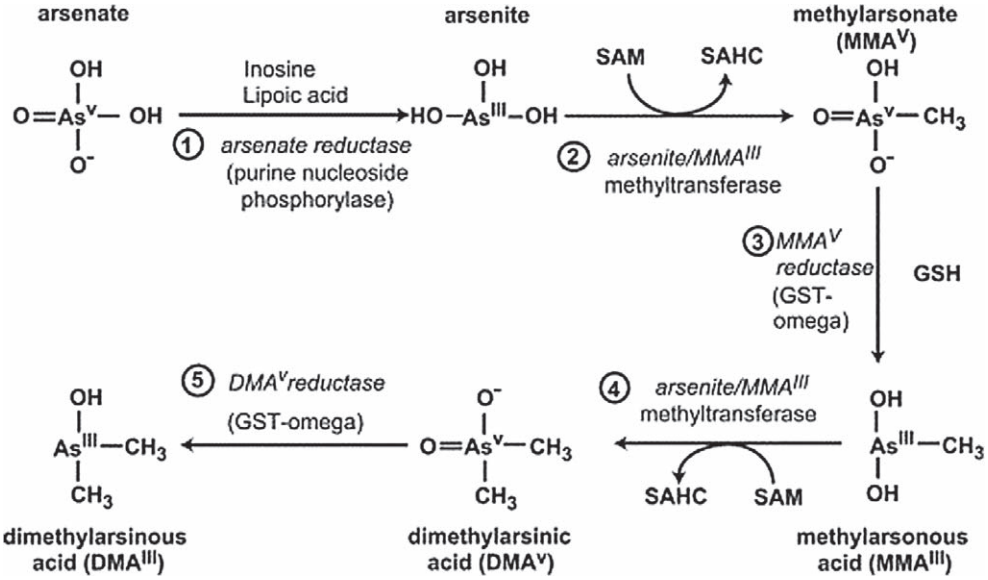

Figure 1. Enzymatic steps in the conversion of inorganic to methylated arsenic in the human [6]. Reprinted with permission from the publisher.

ATO administration in this patient is that it appears to markedly exceed the duration expected from arsenic elimination kinetics derived from whole body tracer studies after administration of small amounts of radioactive inorganic arsenic to normal subjects. Arsenic was shown in these studies to undergo a complex process of elimination from the body consistent with a three component exponential function, with a decrease to undetectable residual levels after approximately 100 days [9], and is inconsistent with the proposed period of retention of arsenic for up to 10 years. It is however possible that the behavior of arsenic may differ and undergo tissue sequestration in a more protracted manner under circumstances where the daily amount of administered inorganic arsenic employed in the therapy of acute promyelocytic leukemia greatly exceeds that employed in tracer studies.

The potential for increased carcinogenicity from arsenic during or following therapeutic administration of ATO is nonetheless an important question, as the amount of inorganic arsenic infused or ingested on a daily basis during treatment is approximately 10–15 times greater than the daily amount ingested in drinking water that is associated with a substantially increased incidence of certain cancers. There are a number of variables that could modify carcinogenic risk of therapeutically administered ATO that require clarification, and relate in particular to whether the overall duration of tissue levels of arsenic species capable of exerting carcinogenic activity during and after treatment are achieved in conventional treatment programs. While the duration of elevated tissue levels of retained arsenic could be evaluated by systematic analysis of tissues removed at elective surgery in successfully treated patients, confirmation of greater than expected arsenic retention would not necessarily constitute proof of carcinogenicity until the threshold level and specific nature of the arsenic compounds with carcinogenic properties are established. A more pragmatic approach for resolving whether a relation exists to increased cancer risk is a collaborative effort to evaluate cancer incidence in the now increasing numbers of long-term survivors of ATO therapy. Confirmation of any increase in cancer risk has obvious implications for assessment of whether the relatively protracted duration of ATO administration currently employed in treatment schedules is excessive, and could be reduced to the minimum duration required for maximum therapeutic activity.

Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

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