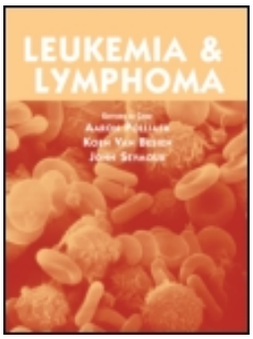

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COMMENTARY

Arsenic: an old enemy now turned friend

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Therapeutic agents that inhibit cellular mechanisms required for growth or survival of neoplastic but not of normal cells can exert targeted anti-neoplastic activity that represents an ideal approach for the treatment of malignant disease. Consequently, there is considerable interest in the molecular basis of responses to agents with this capacity, and an illustrative example is provided by the report of Zhuo and colleagues on the complex biochemical changes that affect arsenic following administration of therapeutic doses of arsenic trioxide (ATO) [1].

ATO is an example of an agent that exerts extremely effective targeted therapy in the treatment of acute promyelocytic leukemia (APL), as it produces remissions followed by sustained freedom from relapse in this highly malignant disorder. The response of APL to ATO closely resembles the response of APL to pharmacological doses of all-*trans* retinoic acid (ATRA), which usually takes the form of a wave of proliferation and differentiation accompanied by loss of self-renewal capacity of the neoplastic clone. The depth of the response to ATO is superior to that with ATRA, as ATO when administered as a single agent induces complete remission (CR) in most patients with newly presenting disease, of whom approximately 80% experience sustained freedom from relapse consistent with cure [2]. The combination of ATO with ATRA and chemotherapy is even more effective, since this approach is associated with sustained freedom from relapse in more than 95% of patients who achieve CR [3].

Both ATO and ATRA induce rapid degradation in APL cells of the PML–RARα chimeric protein that is the product of the fusion gene formed by the characteristic t(15;17) reciprocal chromosomal translocation in APL [4,5]. The concordance between induction of differentiation following ATO or ATRA and their ability to induce degradation of PML–RARα is indicative of the fundamental role that this fusion protein plays in the pathogenesis of APL. ATO produces PML–RARα proteasomal degradation through SUMO-dependent ubiquitination. The alteration in the structure of the PML-derived segment produced during the formation of the PML–RARα fusion protein renders it particularly susceptible to proteasomal degradation following exposure to arsenite, as well as to a number of oxidative processes [5], although administration of ATO appears to be the most practicable option for achieving the desired therapeutic outcome in APL under clinically achievable circumstances. In contrast, ATRA achieves a similar end result by an alternative proteasome-dependent degradation of DNA-bound PML–RARα, and by induction of proteases that cleave PML–RARα. In addition, both ATO and ATRA can activate lysosomal proteolysis (autophagy) of PML–RARα.

Arsenite can also induce apoptosis in human-derived APL cells *in vitro* at concentrations achieved in plasma during treatment, and this observation raises the possibility that such apoptotic effects add to the degradative action on the PML–RARα fusion protein, thereby contributing to the superior therapeutic efficacy of ATO compared to ATRA. The arsenic that is infused as arsenite during treatment with ATO is followed by varying degrees of oxidation to arsenate, and ultimately by methylation to monomethyl and finally dimethyl arsenate by a relatively complex biochemical sequence, as illustrated in Figure 1 [6]. Although monomethyl arsenate formation is regarded as an intermediate in the arsenic detoxification pathway, it has been shown to be cytotoxic to a range of cell lineages *in vitro* at concentrations that are achieved in plasma during ATO therapy, and although it does not appear to result in degradation of the PML–RARα fusion protein, it has the potential to add to toxicity exerted on APL and normal cells during treatment with ATO.

Shifts between the circulation and tissues of individual arsenic chemical species, and the manner in which they act individually or in combination to account for toxicity and therapeutic efficacy after administration of ATO are not well understood. The report by Zhuo *et al.* [1] adds to the mounting body of information about these processes. It had previously been reported that inorganic plus methylated arsenic species achieved peak levels in plasma of the order of 0.3 μM at completion of the usual 2 h infusion of

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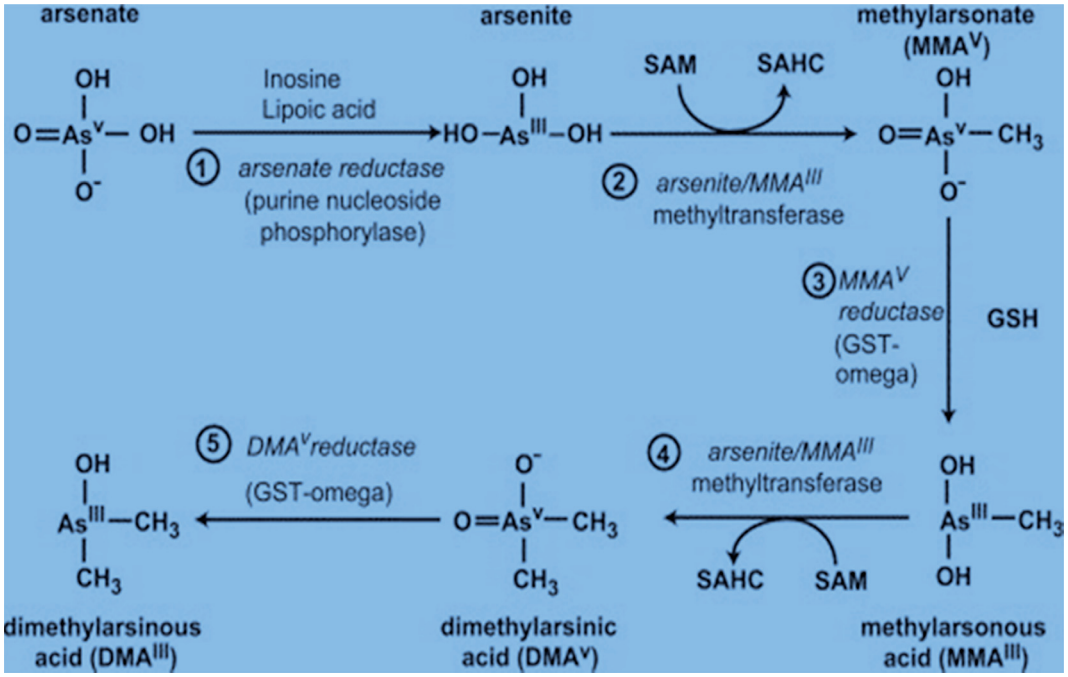

Figure 1. An overview of the sequence of enzymatic steps in the metabolism of arsenic [6]. Reprinted with permission from the publisher.

ATO in patients during treatment for relapsed or refractory APL, after which the levels substantially decreased to nadir values prior to the subsequent daily infusion of ATO [7]. The repeated administration of ATO was accompanied by progressive increases in peak and nadir plasma levels of monomethyl and dimethyl arsenate that presumably reflected accumulation of the methylated products of arsenic during ongoing treatment. Zhou and colleagues have now shown that a similar sequence in nadir plasma levels of arsenic species also occurs in patients with newly diagnosed APL during treatment with ATO.

The value of determining levels of individual arsenic species rather than total arsenic lies in obtaining insight into the contributions made by individual arsenic species to toxicity and efficacy of ATO therapy. It was unfortunately not possible for the findings of Zhuo *et al.* [1] to shed light on the impact of variations in arsenic species on therapeutic efficacy, as all patients achieved a complete remission, and no details were provided on the impact of variations in arsenic species on toxic events. These issues will obviously be the subject of further investigation, and it is important that certain technical and pharmacological factors be taken into consideration for these objectives to be effectively resolved. Levels of arsenic species in plasma determined in the supernatant after precipitation of plasma proteins, as in the current study, may be inaccurate unless full recovery of the arsenic species in the assay sample is achieved, since arsenic species can bind to the proteins that have been precipitated. It is also relevant to note that levels of arsenic in whole blood considerably exceed those in plasma [8], as the total level of arsenic species in erythrocytes is greater than in plasma, to provide an example of the differences that can exist in concentrations of arsenic species between tissue and plasma compartments. Whether quantification of arsenic species in either whole blood or plasma adequately reflects intracellular levels of the same species in APL leukemia-initiating cells and cell types affected by arsenic-mediated toxicity, such as myocardial cells and hepatocytes, also remains to be resolved.

Further clarification of these issues will hopefully lead to modifications to ATO administrative regimens that improve the simplicity and effectiveness of treatment with this agent. Questions that remain to be resolved are whether further pharmacodynamic insights permit modification of currently employed ATO administration schedules to exert optimum efficacy with less protracted and rigorously repetitive treatment, and whether reliable and practical methods can be established to monitor circulating levels of the relevant arsenic species to detect impending toxicity.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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