Arsenic Trioxide and the Phosphoinositide 3-Kinase/Akt Pathway in Chronic Lymphocytic Leukemia

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Simultaneous targeting of the phosphoinositide 3-kinase (PI3K)/Akt pathway increases arsenic trioxide (ATO)-dependent cytotoxicity of chronic lymphocytic leukemia (CLL) cells, whereas it has no significant effects on normal lymphocytes. Combinations of ATO with small molecules that target PI3K and/or Akt may provide a novel approach for the treatment of CLL. Clin Cancer Res; 16(17); 4311–2. ©2010 AACR.

In this issue of Clinical Cancer Research, Redondo-Muñoz and colleagues (1) report on the effects of arsenic trioxide (ATO) on chronic lymphocytic leukemia (CLL) cells. ATO has important antineoplastic properties in vitro and in vivo (2, 3). This agent has been used extensively in the treatment of acute promyelocytic leukemia (APL) in humans, but a major limitation for its use in other hematologic malignancies and solid tumors is the requirement of very high, toxic concentrations for the induction of apoptosis in non-APL cells (2, 3). Redondo-Muñoz and colleagues provide evidence that ATO-induced apoptosis of CLL cells involves inactivation of the kinase Akt and a blockade of the transcriptional factor nuclear factor-κB (NF-κB), as well as upregulation of PTEN and downregulation of XIAP. Notably, ATO treatment of CLL cells was found to induce activation of the c-Jun-NH2 terminal kinase (JNK) kinase, which is essential for the inactivation of Akt and NF-κB and for mitochondrial damage and leukemic cell death (Fig. 1). These findings extend previous work that had shown a critical and essential role for JNK in the induction of ATO-dependent apoptosis in APL cells (4). In addition, they place JNK activation upstream of reactive oxygen species (ROS) in CLL cells, as shown by experiments in which a pharmacologic inhibitor of JNK, or JNK gene silencing, was found to inhibit ROS production by CLL cells. Importantly, the authors of this report also show that combinations of ATO with two different phosphoinositide 3-kinase (PI3K) inhibitors, LY294002 and API-2, result in enhanced apoptosis as compared with treatment with ATO alone. This finding suggests that combinations of ATO with PI3K inhibitors may provide a novel approach to sensitize CLL cells to lower concentrations of ATO that could be achievable in vivo.

The findings of the study of Redondo-Muñoz and colleagues (1) may have important long-term clinical-translational implications for the treatment of CLL. Beyond identifying and characterizing a mechanism by which ATO-dependent inhibition of Akt leads to apoptosis of CLL cells, they raise the possibility of future clinical trials involving combinations of ATO with PI3K inhibitors. Currently, there is intense interest in targeting the PI3K pathway for the treatment of various cancer types, and rapid development of agents for that purpose is ongoing, with several preclinical and early clinical studies under way (5). The findings of Redondo-Muñoz and colleagues (1) are promising, as induction of substantial levels of apoptosis of CLL cells was seen when PI3K inhibitors were combined with low concentrations of ATO (2 μmol/L). Several PI3K (PX-866, XL147, NVP-BKM120, GDC-0941) or dual PI3K/mammalian target of rapamycin (mTOR; SF-1126, NVP-BEZ235, NVP-BGT226, XL765) kinase inhibitors are currently in phase I-II trials for solid tumors (5), whereas one PI3K inhibitor (CAL-101) is currently in phase I studies in hematologic malignancies, including CLL (5). Depending on the outcome of such clinical trials, it is conceivable that combinations of ATO with one or more of these agents could also be explored in future clinical trials in CLL. A particularly important observation in the Redondo-Muñoz study (1) was the fact that, whereas ATO had very potent proapoptotic effects on CLL lymphocytes, it had very minimal effects on normal peripheral blood lymphocytes. This difference was seen at final concentrations of ATO of 2 μmol/L (1). This finding suggests some potential specificity of ATO toward malignant cells as compared with normal lymphocytes, although such mechanisms remain to be investigated and precisely defined in future studies.

Future studies should also determine the effects of ATO on effectors of the mTOR pathway downstream of PI3K/Akt activation in CLL cells. Previous studies have shown that ATO can paradoxically increase mTOR activation and engagement of downstream mTOR effectors in BCR-ABL expressing cells (6) or acute myelogenous leukemia (AML) cells (7); and that combinations...
of ATO with the mTORC1 inhibitor rapamycin result in increased apoptosis and enhanced suppressive effects on primary leukemic progenitors (6, 7). As ATO exhibits suppressive effects on the engagement of PI3K/Akt in CLL cells, it is likely that it will also be eventually found to suppress downstream effectors of the mTOR pathway, but this property will need to be directly examined in future studies. Potential synergistic effects of combinations of ATO with mTOR inhibitors on malignant CLL lymphocytes should also be examined, especially as ongoing clinical efforts are evaluating the effects of mTOR inhibition in the treatment of CLL (8, 9).

In recent years, interest has been renewed in the clinical use of ATO for the treatment of other hematologic malignancies beyond APL (10). The work of Redondo-Muñoz and colleagues (1) provides the basis for further preclinical work that may ultimately lead to clinical trials examining different combinations of inhibitors with ATO for the treatment of CLL. Beyond combinations with inhibitors of the PI3K/Akt/mTOR pathway, it is possible that targeting other key cellular cascades may prove to be of value. In particular, targeting mitogen-activated protein kinase (MAPK) pathways in CLL with specific inhibitors may provide an additional approach to enhance the antileukemic effects of ATO (Fig. 1). Previous studies have shown that treatment of primary chronic myelogenous leukemia cells with combinations of ATO with p38 MAPK inhibitors (11), or treatment of AML cells with combinations of ATO and MEK/ERK inhibitors (12), results in enhanced antileukemic responses in vitro. It would be interesting to examine whether similar enhancing and/or synergistic effects occur in CLL cells, as these effects could provide the rationale for further work and possible clinical evaluation of combinations of ATO with different MAPK inhibitors.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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