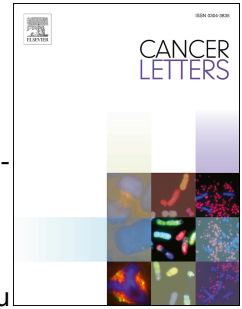


Accepted Manuscript

Novel Combined Ato-C Treatment Synergistically Suppresses Proliferation of Bcr-Abl-Positive Leukemic Cells *In Vitro* and *In Vivo*

Md Wahiduzzaman, Akinobu Ota, Sivasundaram Karnan, Ichiro Hanamura, Shohei Mizuno, Jo Kanasugi, Md Lutfur Rahman, Toshinori Hyodo, Hiroyuki Konishi, Shinobu Tsuzuki, Akiyoshi Takami, Yoshitaka Hosokawa



PII: S0304-3835(18)30431-2

DOI: [10.1016/j.canlet.2018.06.027](https://doi.org/10.1016/j.canlet.2018.06.027)

Reference: CAN 13960

To appear in: *Cancer Letters*

Received Date: 4 March 2018

Revised Date: 31 May 2018

Accepted Date: 18 June 2018

Please cite this article as: M. Wahiduzzaman, A. Ota, S. Karnan, I. Hanamura, S. Mizuno, J. Kanasugi, M.L. Rahman, T. Hyodo, H. Konishi, S. Tsuzuki, A. Takami, Y. Hosokawa, Novel Combined Ato-C Treatment Synergistically Suppresses Proliferation of Bcr-Abl-Positive Leukemic Cells *In Vitro* and *In Vivo*, *Cancer Letters* (2018), doi: 10.1016/j.canlet.2018.06.027.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Abstract

Chronic myelogenous leukemia (CML) accounts for 15-20% of all leukemias affecting adults. Despite recent advances in the development of specific Bcr-Abl tyrosine kinase inhibitors (TKIs), some CML patients suffer from relapse due to TKI resistance. Here, we assessed the efficacy of a novel combinatorial arsenic trioxide (ATO) and cisplatin (CDDP) treatment (Ato-C) in human Bcr-Abl-positive leukemic cells. Combination index analyses revealed that a synergistic interaction of ATO and CDDP elicits a wide range of effects in K562, KU-812, MEG-A2, and KCL-22 cells. Notably, Ato-C synergistically enhanced apoptosis and decreased the survival of both acquired TKI-resistant CML cells and the cells expressing mutant Bcr-Abl^{T315I}. In addition, Ato-C dramatically decreased the phosphorylation level of forkhead transcription factor FOXO1/3a and STAT5 as well as c-Myc protein level. Interestingly, results of gene set enrichment analysis showed that Ato-C significantly downregulates the expression of MYC- and/or E2F1-targets genes. Furthermore, Ato-C significantly suppressed the proliferation of MEG-A2-derived tumor when compared with that following monotherapy *in vivo*. Collectively, these results suggest that combined Ato-C treatment could be a promising alternative to the current therapeutic regime in CML (**180 words**).

Keywords: Arsenic trioxide; cisplatin; combination therapy; Bcr-Abl-positive leukemia; apoptosis.

Download English Version:

<https://daneshyari.com/en/article/8434165>

Download Persian Version:

<https://daneshyari.com/article/8434165>

[Daneshyari.com](https://daneshyari.com)