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

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.

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.