Induction of Cell Death in Gemtuzumab Ozogamicin Resistant and CD33-Positive AML Cells by Enhancing Glutathione-Related Intracellular Oxidation

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BACKGROUND: Gemtuzumab ozogamicin (GO) is a calicheamicin-conjugated CD33-targetting drug and has been used for treating acute myeloid leukemia (AML), but adverse effects and low complete remission rates are shortcoming. We therefore performed an in vitro study to find a favorable multi-drug combination for improvement of GO selectivity and potency.

MATERIALS and METHODS: All of drugs were utilized at minimally effective doses, and CD33-positive and GO-sensitive or -insensitive cell was used, i.e., HL-60 (APL-cell line) and MEG-01 (CML-cell line), respectively.

RESULTS: We first searched successful concomitant drugs with 5 ng/ml of GO in HL-60 cells, and valproic acid (VPA) and suberoylanilide hydroxamic acid (SAHA) was found to be drugs accomplished to augment the GO-inducing cytotoxicity (CI: 2.23 and 1.46, respectively). With GO treatment, intracellular lipid peroxidation products in HL-60 cells were dose-dependently elevated, and it became to be significantly accumulated in cells treated concurrently with VPA or SAHA. While, glutathione (GSH) level in cells with GO alone was also dose-dependently increased, but when cells were treated with GO+VPA/SAHA at cytotoxic levels, GSH could not be increased as a disruption of defense mechanisms against intracellular oxidation. When buthionine sulfoximine (BSO), an inhibitor of GSH synthesis, was added to GO+VPA/SAHA, cytotoxicity was strongly accelerated and reached 2.39-folds of CI in GO+VPA. In case of MEG-01, which exhibited quite higher levels of GSH and P-glycoprotein activity than HL-60, no change was found even in the treatment of GO+VPA+BSO. However, when CSA was added, MEG-01 became to be died. Among all of the drugs, CSA was the vastest influencing factor for GO.

CONCLUSION: These results indicate that GO treatment is greatly regulated by intracellular oxidation status and/or P-glycoprotein activity rather than CD33 expression itself. VPA and CSA are therefore strong accelerators of GO-induced cytotoxicity, by activating/accumulating GSH-related intracellular oxidation. After recognition of cell surface maker CD33 by GO, intracellular action of calicheamicin enhanced by a combination therapy with VPA and/or CSA could work quit effectively even in GO-tolerant AML cells.

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