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Letter to Editor

Drug Switching, a Creative Approach to Leukemia Therapy

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Dear Editor

Leukemia is a heterogenous hematopoietic malignancy associated with chromosomal and molecular abnormalities in hematopoietic stem cells, precursors and progenitors present in bone marrow, peripheral blood and lymph nodes. Leukemia is responsible for about 3% of deaths due to cancer. The uncontrolled hematopoietic cell proliferation is hallmark of leukemia which leads to high mortality. Chemotherapy, immunotherapy, radiotherapy and hematopoietic stem cell transplantation are current therapeutic strategies for the treatment of leukemia, facing with various challenges including drug resistance, side effects, immunologic reactions, relapse and conversion to the accelerated phases in special cases. Therefore, novel agents are needed to achieve safe and high remission rates in the course of the treatment of leukemia (1, 2).

Administration of conventional drugs already approved for other diseases; known as "Drug Switching" or "Drug Repurposing" is developed in recent years to treat various diseases including leukemia, due to their known pharmacokinetic and pharmacodynamics. There are various benefits of drug switching in leukemia including low side effects, high efficacy, accessibility, cost effectiveness, synergism with other drugs and short-term process for approval. Thus, the administration of a repurposed drugs potentially can prevent the toxic effects of current chemotherapeutic agents used in the treatment of leukemia and help increased survival and better prognosis for the patients (3).

Here we aimed to discuss the last advances on drug switching in leukemia, possible challenges and future insights to introducing safe and potent medications against leukemia.

Benzimidazole-based compounds

Benzimidazoles are heterocyclic aromatic compounds [$C_7H_6N_2$] administrated as antihelmintic agents with low toxicity. There are various benzimidazole-derived compounds studied in leukemia. Flubendazole is a benzimidazole compound used as an antinematode which binds to tubulin and inhibits the infection by blocking the cell proliferation, absorption of vital molecules and other essential metabolic pathways related to cell cytoskeleton. In 2010, spagnuolo *et al.* proposed the anti-leukemia effect of flubendazole. Tubulin polymerization is inhibited through binding of flubendazole to tubulin and leads to cytotoxicity.(4) In 2007, khalilzadeh *et al.* introduced albendazole (another benzimidazole-based compound) as an anti-cancer drug for Epothilone-paclitaxel resistant leukemic cells (5). In 2018, walf-vorderwülbecke *et al.* showed the mebendazole inductive role on c-MYB degradation via HSP70 chaperone on acute myeloblastic leukemia (AML), but not normal cell lines (6). The accessibility of benzimidazole-based drugs and their low

rate of toxicity are the golden keys to consider including these drugs in leukemia treatment protocols.

Thiazine-based compounds

Thiazine is an organic compound [C_4H_5NS] with different isoforms which has been used in psychotic diseases. Phenothiazine (PTZ) as a thiazine-class heterocyclic compound is indicated in psychiatric and allergic disorders. The anti-cancer effects of PTZ was come up by lower incidence of some specific cancers among patients with schizophrenia. It is speculated that antiproliferative features of PTZ is exerted via inhibition of calmodulin or blocking the PI3K/AKT pathway. Tsuruo *et al.* showed that PTZ derivate compound inhibits cell proliferation in multidrug-resistant murine leukemia cells (7). Also, in 2004, zhelev *et al.* showed the anti-cancerous effect of PTZ derivate, chlorpromazine, on suppression of cultured leukemia cells. Application of thiazine-based compounds is studying widely in human glioma and neuroblastoma due to crossing from the brain-blood barrier (8). Clomipramine is a tricyclic antidepressant indicated in obsessive disorders. In 1999, xia *et al.* showed anti-leukemia effects of clomipramine on acute myeloid leukemia cell line (HL-60) induced via caspase-3 activation (9).

β-blockers

β-blockers are competitive antagonists of adrenaline (endogenous catecholamines epinephrine) and noradrenaline (endogenous catecholamines norepinephrine). Propranolol is the most commonly used β-blocker which its anti-leukemia potential was proposed by bastani *et al.* in 2010. Their study was performed on human erythroleukemic cell line (K562). The accessibility, wide therapeutic window, and low cost of propranolol are key features of a high-potent drug which could be used in treatment of leukemia (10).

Other compounds

Tanshinone is an anti-inflammatory drug isolated from *Salvia miltiorrhiza*. Anti-cancerous effect of tanshinone was recognized in acute promyelocytic leukemia by chen *et al.*, in 2014. In bioinformatic databases and molecular docking studies, tanshinone was known as an inhibitor of retinoic acid receptor alpha (RARα) expressed on APL cells through the chemical-protein interactions. This study approved the role of the natural compound on drug repurposing in leukemia (11).

Interestingly, there are drug switching between different cancers. Gefitinib is an approved tyrosine kinase inhibitor for Epidermal Growth Factor Receptor (EGFR)-expressing cancers, including breast cancer and lung carcinoma. In 2016, kumar singh *et al.* showed the synergic role of Gefitinib in the treatment of chronic myeloblastic leukemia (CML) by Imatinib. Thus, it suggests that Gefitinib has anti-cancerous potential in Gefitinib-Imatinib combined chemotherapy in CML patients (3).

Development of drug switching is a promising opportunity in treatment of leukemia. The molecular characterization and bioinformatic of current drugs are the critical features to predict the effective agent-protein and agent-nucleic acid interactions which are targeted in drug switching. Also, the molecular modifications help achieve a more specific interaction.

Conflict of Interest: None declared.

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