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Mini-review

Repurposing psychiatric drugs as anti-cancer agents

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ABSTRACT

Cancer is a major public health problem and one of the leading contributors to the global disease burden. The high cost of development of new drugs and the increasingly severe burden of cancer globally have led to increased interest in the search and development of novel, affordable anti-neoplastic medications. Antipsychotic drugs have a long history of clinical use and tolerable safety; they have been used as good targets for drug repurposing. Being used for various psychiatric diseases for decades, antipsychotic drugs are now reported to have potent anti-cancer properties against a wide variety of malignancies in addition to their antipsychotic effects. In this review, an overview of repurposing various psychiatric drugs for cancer treatment is presented, and the putative mechanisms for the anti-neoplastic actions of these antipsychotic drugs are reviewed.

1. Introduction

Cancer is a major public health problem and a leading contributor to the global disease burden [1]. The International Agency for Research on Cancer (IARC) estimates that growth and aging of the population alone are expected to contribute to 21.7 million new cancer cases and 13 million cancer-related deaths by 2030. Hereditary involvement, exposure to radiation and chemicals, unhealthy lifestyles, and other risk factors continue to increase the future burden.

Current chemotherapy treatments mainly include alkylating agents, antimetabolites, antibiotics, topoisomerase inhibitors, and mitotic inhibitors [2], which have remained largely unchanged for three decades. Anticancer agents constantly dominate the US Food and Drug Administration (FDA) drug approval list, although a temporary decline occurred in 2016 [3]. Innovations in cancer drug discovery remain a highly challenging endeavor. Only approximately 10 new cancer drugs are approved by the FDA yearly [4]. The high-cost and time-consuming nature of new drug development represent significant challenges in cancer drug discovery. Several years may be required to prove the efficiency and safety of a new drug. The analysis of 68 randomly selected approved drugs estimated that it takes 15 years and US$ 802 million to bring a new drug to the market. The total pre-approval cost is also increasing at an annual rate of 7.4% [5].

The challenges of developing new drugs suggest the need to explore alternative and novel affordable approaches to treating human cancer. The strategy of converting the indications of existing drugs from one therapeutic area to include the treatment of other diseases, which is also known as “drug repurposing” or “drug repositioning,” shortens the time required for clinical application based on existing previous drug clinical trial results and toxicology testing. This new method of drug discovery has significant advantages over traditional drug development. The use of known drugs and compounds for new indications saves time and cuts the cost of bringing a drug to market. More than 90% of drugs fail the development process. In the last few years, an increasing number of drug companies are now devoting considerable efforts to enhance the efficiency and success rates of drug repositioning. This has created a new strategy for drug discovery creation based on known drugs.

Psychiatric drugs have a long history of clinical use and tolerable

Abbreviations: MSSA, methicillin-susceptible *Staphylococus aureus*; MRSA, methicillin-resistant; *S.* SSRIs, selective, serotonin reuptake inhibitors; MAOIs, monoamine oxidase inhibitors; HDACs, histone deacetylases; CSCs, cancer stem cells; DRs, dopamine receptors.

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safety and have been used as good targets for drug repurposing. For example, thioridazine has well-recognized antimicrobial properties in addition to its antipsychotic activity, which is also common to other phenothiazine analogs [6,7]. It has shown significant in vitro activity against susceptible and multidrug-resistant strains of *Mycobacterium tuberculosis* [8], intracellular methicillin-susceptible *Staphylococcus aureus* (MSSA) [9], methicillin-resistant *S. aureus* (MRSA) [10], and vancomycin-resistant enterococci [11]. The use of thioridazine as an antipsychotic drug has been reduced because of the unfavorable side effects, but investigations and the recent discovery of its antimicrobial properties demonstrate the feasibility and reliability of its clinical efficacy. More studies could be performed to further elucidate other potential clinical uses of this agent. There are also numerous other examples such as haloperidol and its derivative bromperidol, which have currently been repurposed for the treatment of various fungal infections [12].

Psychiatric medications are also promising as a new generation of cancer chemotherapies. Several epidemiological studies have reported that patients with schizophrenia who are receiving antipsychotic drugs have a lower cancer incidence than the general population, suggesting that psychiatric medications might have positive effects on some human cancers. Decreased incidences of prostate, colon, and rectal cancers were observed in patients receiving schizophrenia drugs [13–16]. Psychiatric drugs such as phenothiazines, olanzapine, pimozide, and valproic acid are frequently used in different psychiatric conditions. Further, studies have also showed that these antipsychotic drugs can induce the death of various cancer cells in vitro and in vivo [17–19]. In this review, we present an overview of the repurposing of various psychiatric drugs for cancer treatment and review the putative mechanisms of the anti-neoplastic actions of these psychiatric drugs. In addition, we will discuss the limitations and challenges remaining, including the potential carcinogenicity, controversial clinical studies, and bad tolerance of some psychiatric drugs.

2. Anti-neoplastic properties of psychiatric medications

The high cost of developing new drugs and the increasing severity of the global burden of cancer have increased the interest in the research and development of novel, affordable anti-neoplastic medications. Psychiatric drugs have been used for various psychiatric diseases for decades and are currently reported to have potent anticancer properties against a wide variety of malignancies in addition to their antipsychotic effects.

For more than 100 years, epidemiological studies exploring the association between schizophrenia and cancer have shown conflicting results [20]. A decreased incidence of cancer among patients with schizophrenia compared with that in the general population has been reported in diverse patient populations [21–23]. The evaluation of risk for cancer development in patients with schizophrenia in a large cohort study in an Israeli population demonstrated a lower risk of cancer in patients with than in those without schizophrenia [24]. Another study exploring this association in three Jewish-Israeli populations (Israel, Europe-America, and Africa-Asia) showed that cancer standardized incidence ratios (SIRs) were significantly reduced in patients with schizophrenia for all sites [23]. A population-based study in the US also demonstrated a reduced risk of cancer among persons diagnosed with schizophrenia compared with that in the general population after controlling for known risk and demographic factors [25]. Other studies have identified higher or equivalent relative risk for cancers in patients with schizophrenia than in the general population, contributed by genetic, environmental, and other confounding factors [22]. Studies analyzing selected cancer sites also showed contradictory results, especially for women with breast cancer and men with lung cancer. For example, the increased risk of female-specific cancers such as breast cancer found in some studies may be due to the elevated prolactin effects of psychiatric medications [26,27].

These findings suggest that patients with schizophrenia may have been protected against some cancers based on numerous studies reporting a lower cancer risk in patients with schizophrenia than in the general population [21–25]. One possible explanation is that psychiatric medications may partially decrease the risk of cancer development based on their anti-neoplastic properties [28]. The molecular anticancer mechanisms of antipsychotic agents are yet to be elucidated. Valproic acid is primarily used for bipolar disorder, epilepsy, and migraine headaches. It has also been identified as a promising anti-neoplastic drug based on histone deacetylase (HDAC) inhibition. More than 80 clinical trials have been initiated to evaluate its anticancer properties against different tumors [29]. Phenothiazines are used to treat schizophrenia and psychosis, and they inhibit the growth of cancer cells [28,30–32]. Thioridazine and other phenothiazine drugs have been reported to have anticancer effects mediated by different mechanisms [31]. Sachlos et al. [30] found that thioridazine promotes cancer stem cell differentiation through the dopamine receptor (DR) pathway while Zhelev et al. [31] demonstrated that it inhibits mitochondrial DNA polymerase and decreases ATP production with selectively cytotoxicity and antiproliferative activity in leukemic cells. Another group also found that thioridazine was cytotoxic against the NCI-N87 and AGS gastric cancer cell lines through the mitochondrial pathway [33].

Treatment with the first generation typical antipsychotic drug, penfluridol, was reported to inhibit pancreatic tumor growth by inducing autophagy-mediated apoptosis [34]. Wiklund et al. [35] found that pimozide and the atypical psychiatric medication olanzapine disrupt cholesterol homeostasis to kill cancer cells. There are many other examples of neuroactive drugs with anti-tumor effects including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and monoamine oxidase inhibitors (MAOIs). Gordon et al. [36] showed that SSRIs directly induce apoptosis-associated cytotoxicity in biopsy-like Burkitt lymphoma cells. In another study, paroxetine and sertraline induced a dose-dependent inhibition of the viability and proliferation of human colon cancer cell lines and colorectal cancer cell-xenografted mice [37]. Tricyclic antidepressants were identified to inhibit the growth of neuroendocrine tumors including small cell lung cancer, pancreatic neuroendocrine tumors, and Merkel cell carcinoma [38]. Tranylcypromine is an MAOI used to treat depression that is refractory to numerous other drugs, which fail to treat the symptoms [39]. It has been shown to inhibit BHC110/LSD1 leading to tumor growth inhibition, as an important chromatin modification enzyme capable of demethylating histone [40–43].

These data suggest that psychiatric drugs might have antitumor potential for clinical treatment. These experiments also facilitated the identification of novel targeted strategies that could be rapidly evaluated in patients with a variety of tumors through the repurposing of approved drugs. Psychiatric drugs with potential anti-neoplastic effects are summarized in Table 1. Anti-psychotic drugs kill cancer cells through a variety of pathways including histone deacetylation inhibition, the DR pathway, and disruption of cholesterol homeostasis (see Table 2).

3. Psychiatric medications in brain tumors

Brain tumors are responsible for 2–3% of all cancer-related deaths diagnosed in the US annually [44]. Glioblastoma (GBM) is the most common brain tumor with a devastating and extremely