Advances in the Study of Antitumor Activity and Mechanism of Antipsychotic Drug Brexpiprazole

Jingjing DONG, Yuqiong LI, Ruifen SUN

School of Yunnan University of Traditional Chinese Medicine, Kunming 650500, China

Abstract Antipsychotics such as phenothiazines, pimozide, flupentixol and brexpiprazole have been shown to have good antitumor effects. Brexpiprazole, the successor to aripiprazole, has a better safety profile. Brexpiprazole promotes the death of tumor cells by inhibiting the proliferation of tumor stem cells, resolving the resistance of tumor cells to EGFR-TKIs, and promoting the sensitivity of tumor cells to chemotherapeutic agents, thus inhibiting the development of colorectal, lung, glioblastoma, pancreatic, and gastric cancers. This review focuses on the antitumor effects of antipsychotic drugs, especially the inhibitory effect of brexpiprazole on tumor cells, aiming to provide a theoretical basis for antipsychotic drugs in antitumor field.

Key words Antipsychotics, Brexpiprazole, Cancer therapy

1 Introduction

In recent years, drug reuse has emerged as a promising strategy for identifying novel anticancer drugs, as it has the potential to rapidly develop drugs with established safety and known pharmacokinetic properties[1]. In addition, drug reuse can save a great deal of cost, and studies have shown that it costs about 8.97 million USD to develop a new drug and apply it to the clinic to bring it to the market. Therefore, drug reuse has become a new research direction and has been proven to be feasible. For example, aspirin, as an anti-inflammatory drug, is now widely used for secondary prevention of cerebrovascular ischaemic stroke and cardiovascular disease. Raloxifene is commonly used in the treatment of breast cancer and is now used in the prevention of osteoporotic fractures[2].

Cancer is a complex and dynamic disease that poses a major challenge to human health worldwide. The development of drug resistance and side effects limit the effectiveness of existing treatments, reinforcing the need for new and effective therapies. Some studies have shown that people with schizophrenia appear to have a lower incidence of cancer than the rest of the general population[3]. The Development Risk Assessment Cohort Study found that people with schizophrenia had a lower risk of cancer than non-schizophrenics in a population-based study in Israel[4]. It has also been shown that patients with schizophrenia have a significantly lower standardized incidence of cancer at all loci than non-schizophrenic patients[5]. An explanation for this phenomenon is that antipsychotic drugs taken by people with psychiatric disorders have an anti-tumor effect, thus reducing the risk of cancer[6]. This paper provides a review of the national and international literature on antipsychotic drugs currently used in therapy, with a view to providing a theoretical basis for the application of antipsychotics in the antitumor field.

2 Antipsychotic drugs

Antipsychotic drugs have been the cornerstone of the treatment of schizophrenia since the 1950s, and since then they have evolved rapidly and are now widely used, with indications expanding from schizophrenia to other disorders such as depression, obsessive-compulsive disorder, autism spectrum disorders and sleep disorders[7]. Antipsychotics are subdivided into first generation antipsychotics (FGA) and second generation antipsychotics (SGA). FGA mainly comprise phenothiazines (chlorpromazine, prochlorperazine), thioxanthenes (chlorprothixene, flupentixol), butyrobenzene (haloperidol, penfluridol) and benzamides (sulpiride). The SAG mainly contains clozapine, risperidone, olanzapine, quetiapine, and aripiprazole *et al.* FGA acts mainly by blocking the dopamine D2 receptor, which can easily lead to extrapyramidal reactions and adverse effects such as hyperprolactinemia. SAG acts by blocking 5-hydroxytryptamine 2 receptors, has lower adverse effects compared to FAG, and has a therapeutic effect on negative symptoms such as social withdrawal, which is why SAG is recommended clinically as a first-line therapeutic agent.

Delirium is the most common neuropsychiatric syndrome in cancer patients and is strongly associated with cancer complications and mortality. Delirium occurs in approximately 10% - 30% of cancer patients and in up to 85% of patients when the cancer is in terminal stage[8]. More importantly, the use of chemotherapy, immunotherapy drugs, and medications used in supportive care (such as opioids, antiemetics, and benzodiazepines) can accelerate delirium in patients during cancer treatment[9]. The presence of delirium can adversely affect cancer patients both physically and psychologically, compromising cancer treatment. The use of antipsychotics can control delirium to some extent[10]. At the same time, a large number of studies have shown that antipsychotics can promote tumor cell death by enhancing the efficacy of antitumor drugs, directly killing tumor cells or reversing the resistance to targeted antitumor drugs. Therefore, the use of antipsychotics in the treatment of various types of cancer is scientific and promising.

3 Antitumor effects of antipsychotic anxiety (depressive) drugs

Antipsychotics such as phenothiazines, pimozide, flupentixol and

Received: June 13, 2024 Accepted: September 26, 2024

epirubicin have good therapeutic effects on a variety of malignant tumors such as lung cancer, breast cancer, colorectal cancer, hepatocellular carcinoma and pancreatic cancer. And the mechanism of their occurrence is mainly related to the activation or inhibition of signaling pathways such as EGFR, PI3K/AKT/mTOR, RAF/ERK, and Wnt/β-catenin.

3.1 Phenothiazines Phenothiazines are an important class of antipsychotic drugs commonly used in the treatment of schizophrenia and bipolar disorder[11]. In addition to their use in the treatment of psychiatric disorders, studies have shown that phenothiazines may also act as potential anti-cancer agents, targeting processes involved in tumor growth and metastasis[12]. For example, trichlormethiazide disrupts plasma membrane repair mediated by a member of the membrane-associated protein family (ANXA)[13], and inhibits tumor cell growthinduces G_0/G_1 cell cycle arrest and inhibits tumor cell proliferation and apoptosis[14-15]. Prochlorperazine exhibits synergistic effects on lung cancer cell death *in vivor* and *in vitro*[16-17]. Isoprinosine, on the other hand, promotes apoptosis in tumor cells through AMPK activation and the PI3K/AKT/mTOR signaling pathway[18], or impede proliferation and induce autophagy by increasing LC3II and p62 levels in cancer cell lines[19].

3.2 Pimozide Pimozide, a D2-type dopamine receptor inhibitor, is a typical antipsychotic drug commonly used in the treatment of mental disorders. Recent studies have shown that pimozide can inhibit the growth of a variety of cancer cells, such as breast cancer, colorectal cancer, human osteosarcoma, and hepatocellular carcinoma. Pimozide promotes apoptosis and enhances autophagy in breast cancer cells by activating the RAF/ERK pathway[20]. It also inhibited the proliferation and migration of colon cancer cells HCT116 and SW480 by suppressing the Wnt/β-catenin signaling pathway, as well as suppressing the growth of suppressor tumors in nude mice[21]. Inhibition of Wnt/β-catenin signaling by pimozide also significantly reduced EpCAM expression, thereby effectively inhibiting growth of hepatocellular carcinoma cells[22].

3.3 Flupentixol Flupentixol is widely used as a first class psychotropic drug in the treatment of psychiatric disorders such as schizophrenia, affective apathy, and delusions. In addition to treating psychiatric disorders, flupentixol has shown favorable results in reducing the risk of lung cancer. Studies have shown that patients who use flupentixol for more than one year to treat their illnesses have a reduced risk of developing cancer, and it is important to study the link to lung cancer[23]. In non-small cell lung cancer (NSCLC), flupentixol can inhibit angiogenesis as well as tumor cell invasion and proliferation and migration by interfering with the PI3K/AKT pathway[24]. In addition, flupentixol induced apoptosis in T790M mutant lung cancer cells and synergized with gefitinib to reverse epidermal growth factor (EGFR) inhibitor resistance[25].

3.4 Brexpiprazole Brexpiprazole is a new drug for the treatment of depression and schizophrenia[26]. Bripiprazole was developed as a successor to aripiprazole, which is a modulator of dopamine-serotonin activity with anticancer activity[27]. Bpiripirazole and aripiprazole are chemically and pharmacologically similar and both have anticancer effects, but its lower intrinsic activity at D2 and D3 dopaminergic receptors results in lower cytotoxicity and is more suitable for use in clinical settings[27-28]. Therefore, the use of epirubicin to treat tumors may be an effective and low adverse effect treatment strategy. The types of cancers that can be treated with epirubicin and the mechanisms by which such effects occur are listed below.

3.4.1 Lung cancer. The main means of treating lung cancer in clinic include chemotherapy, radiotherapy, immunotherapy, surgical resection treatment and combined treatment. However, the emergence of drug resistance makes the treatment effect of lung cancer poorer and the overall survival rate lower. Previous studies have shown that EGFR plays an important role in the development of various types of cancers, so it is also an important target for cancer treatment[29-30]. The use of EGFR tyrosine kinase inhibitors (EGFR-TKIs) to inhibit EGFR expression and thereby treat cancer is very promising. However, in non-small cell lung cancer, activation and mutation of the EGFR gene is detected in about 15% to 20% of cases, and wild-type EGFR genes are detected[31-32], accordingly leading to resistance to EGFR-TKIs in non-small cell lung cancer. Osimertinib, an oral third-generation irreversible EGFR-TKIs, is currently considered to be recommended as a first-line agent for the treatment of non-small cell lung cancer[33]. However, long-term use of ositinib may lead to secondary resistance through a number of mechanisms[34]. Experimental studies have shown that the use of epirubicin reduces Survivin expression and reverses resistance to EGFR-TKIs in lung cancer and promotes its antitumor effects[35]. In addition to this, epirubicin also enhances the sensitivity of non-small cell lung cancer cells to 5-fluorouracil and gemcitabine[36].

3.4.2 Colorectal cancer. Colorectal cancer is one of the three most common cancers in the world, with the highest incidence and mortality rates. Currently, the main treatment for colorectal cancer is chemotherapy and radiotherapy, but the survival rate of colorectal cancer patients is still low, and the relative survival rate of stage IV colorectal cancer is only 12%[37]. Bpiripizole was found to inhibit proliferation, adipogenesis, and induce cell cycle arrest in colorectal cancer cells CRC via the AMPK/SREBP1 pathway[38]. Meanwhile, epirubicin likewise inhibited cholesterol synthesis within colon cancer cells HCT116 and SW620, and the mechanism of its occurrence was related to the inhibition of the PI3K/Akt-SREBP2 pathway[39]. In addition, the combination of epirubicin and cetuximab can increase the sensitivity of colon cancer to cetuximab by inhibiting the PI3K-AKT and MAPK-ERK signaling pathways downstream of EGFR, thereby inhibiting the proliferation of colon cancer cells, as well as the growth of trans-

planted tumors in nude mice *in vivor*[40].

3.4.3 Glioblastoma. Glioblastoma is a primary brain tumor that accounts for 60% to 70% of glial brain tumors[41-42]. Due to its highly infiltrative growth, the prognosis is poor. Moreover, glioblastoma is highly resistant to chemotherapeutic agents, which is a serious threat to human life and health. Cancer stem cells (CSCs) have a high tumor initiating capacity and are resistant to chemotherapeutic agents, and play a role in chemotherapy resistance[43-44]. *In vitro* studies show that application of epirubicin increases the sensitivity of glioma stem cells (GSCs) to third-generation EGFR-TKIs ositinib by inhibiting Survivin expression.

3.4.4 Pancreatic cancer. Pancreatic cancer is one of the common malignant tumors of the digestive tract[45]. Pancreatic cancer is often detected at an advanced stage and misses the best treatment period; only 15% to 20% can be surgically removed at the time of diagnosis, but the treatment outcome is poor, with a 5-year survival rate of 10%[46]. *In vitro* cellular and *in vivor* animal experiments demonstrated that epirubicin could significantly promote cell death of pancreatic cancer cells PANC-1 and PSN-1 and inhibit the growth of transplanted tumors in nude mice *in vivor* by decreasing the expression of Sox2 and Survivin[36]. In addition, Bpirubicin promotes the *in vitro* antitumor activity of ositinib and the death of pancreatic cancer cells PANC-1[35].

3.4.5 Gastric cancer. The incidence and mortality rates of stomach cancer are among the highest in the world, and the latest data from GLOBOCAN show that there are as many as 1.03 million new cases of lung cancer and 782 000 deaths worldwide[47]. Lysine-specific histone demethylase 4A (KDM4A) is an important epigenetic enzyme. Studies have shown that KDM4A is highly expressed in clinical gastric cancer tissues and positively correlates with poor prognosis of gastric cancer, and that high expression of KDM4A also promotes the growth of gastric cancer *in vitro*. Bpiprazole inhibits the activity of KDM4A by targeting its binding, thereby down-regulating the transcript and protein levels of c-Myc, and ultimately inhibiting the growth of gastric cancer *in vivor* and *in vitro*.[48].

4 Conclusions

Antipsychotic drugs may promote tumor cell death by enhancing the efficacy of antineoplastic drugs, reversing resistance to antineoplastic drugs, or directly killing tumor cells. Currently, antipsychotics that have been studied for cancer treatment include phenothiazines (trichlormethiazide, prochlorperazine, chlorpromazine), pimozide, flupentixol, aripiprazole, and bpiripiprazole. Among them, bpiripizole is very promising for cancer treatment due to its low adverse effect profile. In the future, researchers can focus on ipipiprazole to study the antitumor effects of antipsychotics and the mechanism of antitumor effects, which will provide more hope and possibilities for drug reuse of antipsychotics.

References

[1] SINGHAL S, MAHESHWARI P, KRISHNAMURTHY PT, *et al.* Drug repurposing strategies for non-cancer to cancer therapeutics[J]. Anti-cancer Agents in Medicinal Chemistry, 2022, 22(15): 2726-2756.

[2] CHEN Y. Discovery of phenothiazines as anti-endometrial cancer compounds[D]. Shanghai: East China University of Science and Technology, 2024. (in Chinese).

[3] CHOU FH, TSAI KY, SU CY, *et al.* The incidence and relative risk factors for developing cancer among patients with schizophrenia: A nine-year follow-up study[J]. Schizophrenia Research, 2011, 129(2-3): 97-103.

[4] BARAK Y, ACHIRON A, MANDEL M, *et al.* Reduced cancer incidence among patients with schizophrenia[J]. Cancer, 2005, 104(12): 2817-2821.

[5] GRINSHPOON A, BARCHANA M, PONIZOVSKY A, *et al.* Cancer in schizophrenia: Is the risk higher or lower[J]. Schizophrenia Research, 2005, 73(2-3): 333-341.

[6] FOND G, MACGREGOR A, ATTAL J, *et al.* Antipsychotic drugs: Pro-cancer or anti-cancer: A systematic review[J]. Medical Hypotheses, 2012, 79(1): 38-42.

[7] MELTZER HY. Update on typical and atypical antipsychotic drugs[J]. Annual Review of Medicine, 2013(64): 393-406.

[8] BREITBART W, ALICI Y. Agitation and delirium at the end of life: "We couldn't manage him"[J]. Jama, 2008, 300(24): 2898-2910.

[9] LAWLOR PG, GAGNON B, MANCINI I L, *et al.* Occurrence, causes, and outcome of delirium in patients with advanced cancer: A prospective study[J]. Archives of Internal Medicine, 2000, 160(6): 786-794.

[10] VAN DEN BOOGAARD M, SCHOONHOVEN L, VAN ACHTERBERG T, *et al.* Haloperidol prophylaxis in critically ill patients with a high risk for delirium[J]. Critical Care (London, England), 2013, 17(1): R9.

[11] EDINOFF AN, ARMISTEAD G, ROSA CA, *et al.* Phenothiazines and their evolving roles in clinical practice: A narrative review[J]. Health Psychology Research, 2022, 10(4): 38930.

[12] XI H, WU M, MA H, *et al.* Repurposing fluphenazine to suppress melanoma brain, lung and bone metastasis by inducing G_0/G_1 cell cycle arrest and apoptosis and disrupting autophagic flux[J]. Clinical & Experimental Metastasis, 2023, 40(2): 161-175.

[13] HEITMANN ASB, ZANJANI AAH, KLENOW MB, *et al.* Phenothiazines alter plasma membrane properties and sensitize cancer cells to injury by inhibiting annexin-mediated repair[J]. The Journal of Biological Chemistry, 2021, 297(2): 101012.

[14] ZHANG X, DING K, JI J, *et al.* Trifluoperazine prolongs the survival of experimental brain metastases by STAT3-dependent lysosomal membrane permeabilization[J]. American Journal of Cancer Research, 2020, 10(2): 545-563.

[15] FENG Z, XIA Y, GAO T, *et al.* The antipsychotic agent trifluoperazine hydrochloride suppresses triple-negative breast cancer tumor growth and brain metastasis by inducing G_0/G_1 arrest and apoptosis[J]. Cell Death & Disease, 2018, 9(10): 1006.

[16] SAD K, PARASHAR P, TRIPATHI P, *et al.* Prochlorperazine enhances radiosensitivity of non-small cell lung carcinoma by stabilizing GDP-bound mutant KRAS conformation[J]. Free Radical Biology & Medicine, 2021(177): 299-312.

[17] CHEW HY, DE LIMA PO, GONZALEZ CRUZ JL, *et al.* Endocytosis inhibition in humans to improve responses to ADCC-mediating antibodies [J]. Cell, 2020, 180(5): 895-914.

[18] TAN X, GONG L, LI X, *et al.* Promethazine inhibits proliferation and

promotes apoptosis in colorectal cancer cells by suppressing the PI3K/AKT pathway[J]. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie, 2021(143): 112174.

[19] AVENDAÑO-FÉLIX M, AGUILAR-MEDINA M, BERMUDEZ M, *et al.* Refocusing the use of psychiatric drugs for treatment of gastrointestinal cancers[J]. Frontiers in Oncology, 2020(10): 1452.

[20] JIANG G, ZHOU X, HU Y, *et al.* The antipsychotic drug pimozide promotes apoptosis through the RAF/ERK pathway and enhances autophagy in breast cancer cells[J]. Cancer Biology & Therapy, 2024, 25(1): 2302413.

[21] REN Y, TAO J, JIANG Z, *et al.* Pimozide suppresses colorectal cancer via inhibition of Wnt/β-catenin signaling pathway[J]. Life Sciences, 2018(209): 267 – 273.

[22] FAKO V, YU Z, HENRICH CJ, *et al.* Inhibition of wnt/β-catenin signaling in hepatocellular carcinoma by an antipsychotic drug pimozide [J]. International Journal of Biological Sciences, 2016, 12(7): 768 – 775.

[23] CHAI Y, CHU RYK, HU Y, *et al.* Association between cumulative exposure periods of flupentixol or any antipsychotics and risk of lung cancer [J]. Communications Medicine, 2023, 3(1): 126.

[24] DONG C, CHEN Y, LI H, *et al.* The antipsychotic agent flupentixol is a new PI3K inhibitor and potential anticancer drug for lung cancer[J]. International Journal of Biological Sciences, 2019, 15(7): 1523 – 1532.

[25] LI H, TONG CW, LEUNG Y, *et al.* Identification of clinically approved drugs indacaterol and canagliflozin for repurposing to treat epidermal growth factor tyrosine kinase inhibitor-resistant lung cancer[J]. Frontiers in Oncology, 2017(7): 288.

[26] CORRELL CU, SKUBAN A, OUYANG J, *et al.* Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: A 6-week randomized, double-blind, placebo-controlled trial [J]. The American Journal of Psychiatry, 2015, 172(9): 870 – 880.

[27] SUZUKI S, OKADA M, KURAMOTO K, *et al.* Aripiprazole, an antipsychotic and partial dopamine agonist, inhibits cancer stem cells and reverses chemoresistance [J]. Anticancer Research, 2016, 36(10): 5153 – 5161.

[28] FRANKEL JS, SCHWARTZ TL. Brexpiprazole and cariprazine: distinguishing two new atypical antipsychotics from the original dopamine stabilizer aripiprazole[J]. Therapeutic Advances in Psychopharmacology, 2017, 7(1): 29 – 41.

[29] YARDEN Y, PINES G. The ERBB network: At last, cancer therapy meets systems biology [J]. Nature Reviews Cancer, 2012, 12(8): 553 – 563.

[30] SIGISMUND S, AVANZATO D, LANZETTI L. Emerging functions of the EGFR in cancer[J]. Molecular Oncology, 2018, 12(1): 3 – 20.

[31] YUN CH, BOGGON TJ, LI Y, *et al.* Structures of lung cancer-derived EGFR mutants and inhibitor complexes: mechanism of activation and insights into differential inhibitor sensitivity[J]. Cancer Cell, 2007, 11(3): 217 – 227.

[32] COLLISSON EA, CAMPBELL JD, BROOKS AN, *et al.* Supp info: Comprehensive molecular profiling of lung adenocarcinoma[J]. Nature, 2014, 511(7511): 543 – 550.

[33] SORIA J C, OHE Y, VANSTEENKISTE J, *et al.* Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer[J]. The New England Journal of Medicine, 2018, 378(2): 113 – 125.

[34] MURTUZA A, BULBUL A, SHEN JP, *et al.* Novel third-generation EGFR tyrosine kinase inhibitors and strategies to overcome therapeutic resistance in lung cancer[J]. Cancer Research, 2019, 79(4): 689 – 698.

[35] SANOMACHI T, SUZUKI S, TOGASHI K, *et al.* Brexpiprazole Reduces Survivin and Reverses EGFR tyrosine kinase inhibitor resistance in lung and pancreatic cancer[J]. Anticancer Research, 2019, 39(9): 4817 – 4828.

[36] SUZUKI S, YAMAMOTO M, TOGASHI K, *et al.* *In vitro* and *in vivor* anti-tumor effects of brexpiprazole, a newly-developed serotonin-dopamine activity modulator with an improved safety profile[J]. Oncotarget, 2019, 10(37): 3547 – 3558.

[37] MILLER K D, NOGUEIRA L, DEVASIA T, *et al.* Cancer treatment and survivorship statistics, 2022[J]. CA: A Cancer Journal for Clinicians, 2022, 72(5): 409 – 436.

[38] LI T, LIU X, LONG X, *et al.* Brexpiprazole suppresses cell proliferation and de novo lipogenesis through AMPK/SREBP1 pathway in colorectal cancer[J]. Environmental Toxicology, 2023, 38(10): 2352 – 2360.

[39] LI T, LONG XY, LIU XJ, *et al.* Effect and mechanism of brexpiprazole on cholesterol synthesis of human colorectal cancer cell lines HCT116 and SW620[J]. Shandong Medical Journal, 2023, 63(33): 7 – 10. (in Chinese).

[40] LONG XY. Mechanisms of inhibition of colon cancer by etiprazole and increased sensitivity to cetuximab[D]. Nanchong: North Sichuan Medical College, 2023. (in Chinese).

[41] OMURO A, DEANGELIS LM. Glioblastoma and other malignant gliomas: A clinical review[J]. Jama, 2013, 310(17): 1842 – 1850.

[42] THOMAS AA, BRENNAN CW, DEANGELIS LM, *et al.* Emerging therapies for glioblastoma [J]. JAMA Neurology, 2014, 71(11): 1437 – 1444.

[43] BECK B, BLANPAIN C. Unravelling cancer stem cell potential[J]. Nature Reviews Cancer, 2013, 13(10): 727 – 738.

[44] MAUGERI-SACCÀ M, VIGNERI P, DE MARIA R. Cancer stem cells and chemosensitivity[J]. Clinical Cancer Research : An Official Journal of the American Association for Cancer Research, 2011, 17(15): 4942 – 4947.

[45] DEL CHIARO M, SUGAWARA T, KARAM SD, *et al.* Advances in the management of pancreatic cancer[J]. BMJ (Clinical Research ed), 2023(383): e073995.

[46] STROBEL O, NEOPTOLEMOS J, JÄGER D, *et al.* Optimizing the outcomes of pancreatic cancer surgery[J]. Nature Reviews Clinical Oncology, 2019, 16(1): 11 – 26.

[47] FERLAY J, COLOMBET M, SOERJOMATARAM I, *et al.* Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods [J]. International Journal of Cancer, 2019, 144(8): 1941 – 1953.

[48] LI A. Brexpiprazole targeting KDM4A inhibits the growth of gastric cancer[D]. Zhengzhou: Zhengzhou University, 2022. (in Chinese).