THE NEUROPROTECTIVE EFFECTS OF ANTICANCER DRUGS ON PARKINSON'S DISEASE

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INTRODUCTION

Parkinson's disease is a condition involving the progressive depletion of dopaminergic neurons in the basal ganglia, particularly in the substantia nigra, and formation of Lewy bodies. The current therapeutic options for this condition target symptomatic relief and no therapeutic modality can arrest the neurodegenerative process. Levodopa is the drug of choice.

There is a significant overlap between the upregulation of genes in neurodegenerative diseases and downregulation in cancer and vice-versa. Genes such as Parkin, p53, JAK/STAT pathway, c-Abl, α-Synuclein and Tyrosine kinase contribute to cancer or neurodegeneration, depending on the cellular context.

MATERIALS AND METHODS

We searched PubMed, Cochrane, Wiley Online Library, and NCB and found 19 articles which served the purpose of our research, by using the key words "neurodegenerative diseases", "Cancer" and "Parkinson's", the combination "anticancer drugs" and "parkinson's disease" was also used.

We assembled a list of drugs, factoring out the ones that have only been tested in vitro and chose which were still in trial. We included the drugs which were already on the market for a different motive and had been repurposed. In the end, we narrowed down a list of drugs with common purposes in both conditions.

RESULTS

- ★ Both Imatinib and Nilotinib are tyrosine kinase inhibitors though nilotinib has shown to have increased specificity for c-Abl, potency, and high BBB penetrance making it attractive for usage. A Phase I clinical trial reported that low doses of nilotinib enter the brain and promote the degradation of aSyn and tau in animal models, a phase 2A study in patients with advanced PD failed to demonstrate efficacy, suggesting additional studies are necessary.
- ★ The JAK inhibitor, Ruxolitinib, on the other hand could block oxidative stress induced cell death by IL-13.
- ★ A drug used for melanoma called Dabrafenib was shown to prevent dopaminergic neuronal loss in a mouse model significantly hence confirming the neuroprotective effects in vivo.
- ★ A small molecule, Anle138b has shown to target α-synuclein aggregation in various models. In vivo, an alteration in formation of disease-associated oligomers to smaller oligomers and monomers by anle138b treatment for α-syn has been noticed. In animals, anle138b has been shown to efficiently cross the blood-brain barrier.

DRUG	DRUG CLASS	RESULT	CLINICAL USE
Imatinib	Tyrosine kinase inhibitor	↓ dopaminergic neuronal death; Improvement in locomotive deficits	Chronic Myelogenous Leukemia
Nilotinib	2nd gen tyrosine kinase inhibitor	improvement in motor and cognitive performances	CML and other blood cancers
Ruxolitinib	JAK inhibitor	↓JAK1 and JAK3, ↓inflammation	Myelofibrosis
Dabrafenib	Kinase inhibitor	Prevention of dopaminergic neuronal loss	BRAF mutated metastatic melanoma
Anle138b	oligomeric aggregation inhibitor	↓α-synuclein aggregated species without affecting normal α-synuclein	Melanoma

CONCLUSION

Upon accumulation of preclinical and clinical evidence, the critical role of pathways such as Fyn, JAK inhibitors, and c-Abl inhibitors were highlighted that could serve as a potential therapeutic target in many aspects of PD pathophysiology including neuroinflammation, α-synuclein phosphorylation, oxidative stress, and dopaminergic neuronal loss. Our review suggests that these inhibitory pathways may be a potential therapeutic option for PD patients, however, more clinical studies are necessitated.

The repurposing of chemotherapeutic drugs, such as Imatinib, Nilotininb, Ruxolitinib, Dabrafenib, and Anle 138b for PD could unravel new possibilities in urgent necessity of drug development of this neurodegenerative disorder.

References: 1) PMID: 33346940 2) PMID: 23604588, 3) PMID: 35500536 4) PMID: 30137437