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Repurposing of L-Type Calcium Channel Blockers for Cancer Treatment

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ABSTRACT: Though the traditional strategies for cancer treatment are still used but they are associated with many drawbacks as developing resistance, toxicities especially at high doses, and lack the financial ability to cover the costs of current chemotherapeutic agents. A number of already exist and approved drugs undergo multiple pre-clinical and clinical studies and were found to have promising anti-tumor action, so they can be repurposed to treat cancer. This strategy are considered cost-saving as compared to discovering and developing a new compound to treat cancer, enable to overcome resistance as they target pathways that differ from those of traditional therapies, and its combination with low dose of the approved anticancer drugs will minimize the adverse effects. Calcium channel blockers are among the drugs that are still being investigated to discover their anti-cancer actions.

KEYWORDS: calcium channel blockers, cancer, drug repurposing.

INTRODUCTION

1. Concept of Drug Repurposing in Cancer

Drug repurposing means using an already existing and approved drug for an indication other than the approved uses (1). This idea is especially important for treating resistant diseases; hence, researchers apply this strategy for treating cancer that is especially advanced and resistant to traditional modalities of treatment (2). The main reasons for drug repurposing for cancer management is to minimize the cost, time, and risk that are associated with developing new discovered drugs. As the safety profile, pharmacokinetic data and toxicological aspect of drug are known. Moreover, their cost will be much lower than developing new drug or modality for treating cancer (3).

Certain drugs have been repurposed and received FDA approval for treating human cancers, while others are still in the development phase (4, 5).

Table (1) shows the FDA-approved drugs that repurposed for cancer (5).

Drug	Original-use	Cancer indication-Year of approval
Arsenic Trioxide	Industrial uses	Acute pro-myelocytic leukemia- (2000)
Celecoxib	Osteoarthritis & Rheumatoid arthritis	Familial-adenomatous polyposis (1999)
Mitotane	Adrenal-disorders	Adrenocortical carcinoma - 1970
Thalidomide	Erythema-nodosum leprosum	Multiple myeloma- 2006
Tretinoin	Topical for severe-acne	Acute- promyelocytic leukemia-1995

2. L- Type Calcium-channel blockers (CCBs):

Previously and up to the present, L-type CCBs were used to treat cardio-vascular diseases by their ability to antagonize calcium channels mainly L-type calcium channel (6). They approved to treat cardio-vascular disorders mainly hypertension, ischemic heart disease, and tachyarrthymias (7,8). Also CCBs have specific indications that yet not approved by FDA, such as Raynaud-phenomenon, anal fissures, pulmonary hypertension, sub-arachnoid hemorrhage, & migraine headaches (9).

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CCBs are categorized into 2 main classes according to their chemical-structure and their pharmacologic-action (10).The first class is non-dihydropyridines: phenylalkylamine (verapamil) & benzothiazepine (diltiazem) where approved to treat chronic-stable and vasos-pastic angina, hypertension, and as anti-arrhythmic agents. The second class is dihydropyridines, the FDA-approved members are (amlodipine, nifedipine, nicardipine, nisoldipine, felodipine, isradipine, levamlodipine, nimodipine). Their approved uses are coronary-artery diseases, hypertension, chronic stable angina, prinzmetal-angina, and subarachnoid hemorrhage (11, 12).

3. Mechanisms of L-Type CCBs in Cancer:

The proposed mechanisms that enable CCBs to act as anti-cancer are illustrated by a number of pre-clinical studies as the followin:

1. Multidrug-Resistance (MDR) Reversal:

Overexpression of drug efflux-pumps by some cancer cells as example "P-glycoprotein" (P-gp) that pump chemotherapeutic agents out of the cells and so reducing effectiveness of treatment (13). Verapamil as well as diltiazem inhibit P-gp-activity hence increasing intra-cellular anti-cancer agents concentrations so enhancing efficacy. Verapamil was the first one investigated as an MDR-modulator (14).

2. Inhibition the proliferation of Cancer Cell:

Calcium ions are noted to play substantial roles in cell-proliferation, cell-cycle progression, and signal transduction (15). So that, blockage of calcium-influx may protract tumor-cell growth, induce cell-cycle arrest, moreover the might contribute to apoptosis in certain types of cancer (16).

3. The ability to oppose metastasis:

Calcium ions play notable role in cell-migration, invasion, and metastasis. CCBs may cause crucial decline to these processes by interrupting pathways that depend on calcium-ions and involved in tumor spreading (17).

4. Efficacy Enhancement of Chemotherapy and Radiotherapy:

A number of Pre-clinical studies found that CCBs may sensitize cancer cells to chemotherapy and also may rise the responsiveness to radiation therapy (18).

4. Pre-clinical Studies involving L-type CCBs to be investigated as anti-cancer agents.:

Table (1) represent a number of published pre-clinical studies which investigated the anti-cancer capacity of L-type-CCBs especially in tumors that are resistant to chemotherapy.

Table (2): Pre-clinical studies involving use L-type CCBs as anti-cancer agents.

L type-CCBs	Cancer-type	Cell-line	Results	Ref.
Diltiazem, Nifedipine, Verapamil.	lung cancer	A549-chemoresistant	Induction of apoptosis & autophagy	19
Amlodipine+ Lercanidipine	Gastric adeno-carcinoma	AGS, MKN-45	Decrease proliferation, sensitization to doxorubicin	20
Amlodipine	Breast cancer	MCF-7, MDA-MB-231	Apoptosis induction, inhibition of proliferation & invasion, also decline colony-formation.	22
Amlodipine	Non-small cell lung-cancer	A549-cell line A549- xenograft mice)	Suppressed proliferation and cell-cycle arrest; enhanced gefitinib efficacy	23
Amlodipine	Esophageal-squamous-cell carcinoma	Eca109, KYSE-450, & xenograft-models	Induce autophagy & apoptosis and inhibit migration through endoplasmic-reticulum stress induction.	24
Amlodipine	Head & neck squamous-carcinoma	PCI-13, SCCVII-cell lines & Xeno-graft model	Decline in proliferation, reduce tumor-growth in xenograft-models, and decrease immunosuppression	25
Amlodipine	Pancreatic cancer	Mice-xenograft models	Reversal of gemcitabine-resistance and inhibition of tumor-progression	26
Lercanidipine + Doxorubicin	Gastric-cancer	Gastric-cancer xenografts	Combined-therapy reduced growth of tumor-mass compared with doxorubicin-mono-therapy	27

5. Human Clinical Studies:

In human, clinical proof is limited, and no L-type-CCB is currently has approval as an anti-cancer agent. Most results comes from pre-clinical studies, and a few "early-phase" clinical investigations were found. So that, in the future, there must be adequate clinical-studies investigating the role of L-Type CCBs as an adjuvant to conventional chemotherapy especially in metastatic resistant cancer (28, 29).

CONCLUSION

From the available pre-clinical studies, we conclude that L-type CCBs are promising agents in field of oncology as they have attractive factors such as their availability with low cost and their safety-profile. Despite this, further randomized clinical-trials are needed to optimize dose, pharmacokinetic-data, and their possible combination with other cancer therapies according to cancer type and stage. Moreover, there is a need to study patient-derived-biomarkers especially that are modulated by CCBs to further understand molecular-mechanisms and changes that happen in tumor-microenvironment. Finally, if sufficient clinical-studies become available, L-type CCBs can be used successfully in combination with other anti-cancer- strategies to enhance their efficacy for treating advance resistant- cancer.

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